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THE PROTEIN METABOLISM OF AN INFANT*

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The diversity of opinion among pediatricians concerning the digestion of protein has led to much discussion, and although certain phases of the question have been cleared up, there still remains much to explain. Recently Mendel and his co-workers have attacked the problem from a new angle in their brilliant studies in growth and the part played by the various members of the protein group in affording a "growth impulse" in growing animals. Studies of the effect of protein on the energy metabolism of infants have been carried on in Professor Lusk's laboratories at Cornell University Medical College by Howland[1] and more recently Hoobler and Murlin[2] have added much to our knowledge of this phase of the subject.

Although clinical symptoms of protein indigestion have been recognized by many clinicians, mainly of the American schools, an equally large number maintain that protein is harmless even in large amounts. The two groups may be roughly divided into those who use raw milk in infant feeding on the one hand, and those who use principally boiled or heated milk on the other hand. The question of the age of the infant also plays a part in the quantity of protein that may be given without resulting in symptoms of indigestion. It may be said, in general, the younger the infant is, the more frequently do symptoms of indigestion appear when large doses of protein are given. After the age of 5 or 6 months, the danger of giving an average infant more protein than it can tolerate diminishes rapidly. Exceptions, however, may be found in the abnormally strong and vigorous infant who can digest more, or the weak infant who can digest relatively less, at a given age. A third factor which seems to influence the ability of the infant to digest protein is presence of disease in the intestines. That

* Submitted for publication May 18, 1916.

* From the Children's Medical Department of the Massachusetts General Hospital.

1. Howland: Tr. Fifteenth Internat. Cong. Hyg. and Demog., 1912, ii, 438.

2. Murlin and Hoobler: Am. Jour. Dis. Child., 1915, ix, 81. Hoobler: Am. Jour. Dis. Child., 1915, x, 153.

is not confined to protein alone, but applies to all the other food elements. Finally, clinical symptoms of indigestion which apparently are the result of too much protein in the food are not so common as those which are brought about by an excess of carbohydrates or fat in the food. These symptoms depend in part on whether the milk is raw or sterilized. Since the only definite outward signs of protein indigestion are casein curds in the stools, and since boiling the milk causes these curds to disappear from the stools,[3] casein curds are rarely seen in communities which sterilize all their milk, and the diagnosis of protein indigestion is made more difficult than ever.

Selter[4] described a picture of intoxication from protein in which there was an excursion of body temperature from 37 C. (98.6 F.) to 34 C. (93.2 F.) (subnormal), slow pulse and superficial respiration. The color of the skin became bluish gray. He found that the urine contained a kenotoxin which, when injected into mice, resulted in symptoms similar to those which he described in babies. Hoobler[5] subsequently found that when a large amount of protein was given to an infant, "the child no longer took interest in his surroundings, and gradually entered into a state of semistupor. The pulse was slower and there were times when the respirations were slightly irregular. The stupor continued for a few days after the observations ceased," after which "it gradually lessened, so that within one week the child was normal again and began to gain weight." Monrad[6] and Morse[7] believe that casein is not harmless and may cause indigestion, while Salge[8] speaks of a condition in which he is unable to give specific clinical symptoms, as *Eiweissnahrschaden*. Holt and Levene[9] observed a rise in temperature in five instances during the administration of a "synthetic food" containing 6 per cent. of casein, and a retention of chlorids for three or four days preceding the rise in temperature. They draw attention to the similar rise in temperature described by Vaughan after the parenteral injection of protein. Finkelstein and his followers, on the other hand, believe that casein is harmless, while Howland[10] and others say that casein curds in the stools are of "limited, if any, pathological importance, but rather depend on physical conditions in the gastro-intestinal tract."

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3. Brenneman: Am. Jour. Dis. Child., 1911, i, 341. Ibrahim: Monatschr. f. Kinderh., 1911, x, 55.
4. Selter: Deutsch. med. Wchnschr., 1908, p. 512.
5. Hoobler: Footnote 2, second reference.
6. Monrad: Monatschr. f. Kinderh., 1911, x, 244.
7. Morse: New York Med. Jour., 1913, xcvii, 477.
8. Salge: Ztschr. f. Kinderh., 1912, 112.
9. Holt and Levene: Med. Klin., 1913, ix, 258.
10. Howland: Am. Jour. Dis. Child., 1913, v, 390.

An analysis of the figures of previous investigators does not give any explanation of the clinical symptoms which are seen in practice, and it was with the hope of answering some of the clinical questions that this investigation was undertaken. Although the figures obtained do not answer any questions from the point of view of the clinician, they contain many interesting facts which will be commented on later, and serve to substantiate or amplify the findings of previous investigators. We believe that they are of sufficient importance to record.

F. W. L. was born Dec. 4, 1913, at full term. During the first three months of life he was fed on modified milk. On March 12, 1914, he came to the outpatient department of the Massachusetts General Hospital with colic and

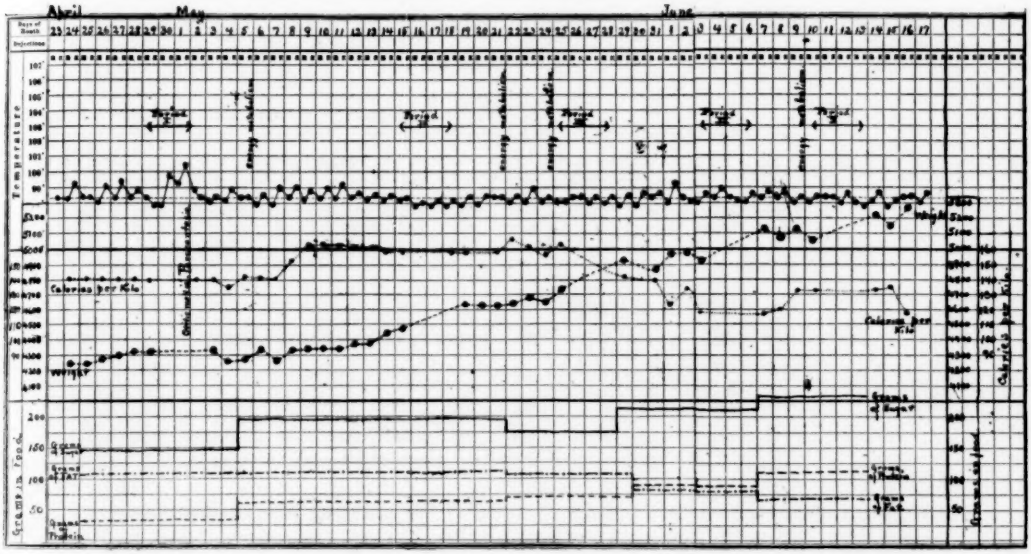

Fig. 1.—Metabolism record of F. W. L., covering a period of nearly two months, showing the intake of fat, protein and sugar from day to day, its value in calories per kilogram of body weight, the increase in weight of the infant and the variation in body temperature.

constipation, and weighing 4,280 gm. His formula was changed from time to time, the last one being fat 2.5, lactose 6, protein 1.6, 4 ounces, 7 feedings. Just before entering the children's ward, April 23, 1914, at the age of 4½ months, he weighed 4,315 gm. Physical examination showed that he was poorly developed and poorly nourished with flabby musculature, but was otherwise normal, the only fact worthy of note being that the liver dulness extended from the fourth intercostal space to 3 cm. below the edge of the ribs in the nipple line. Figure 1 shows the temperature, weight curves, calories and food per twenty-four hours, given during the time he was in the hospital, and at the different periods investigated. The periods in which the food and excreta were examined were each of three days' duration, the stools at the beginning and end of each period were marked off with charcoal. In one instance the food was changed twenty-four hours before the period commenced, and

in all others several days had elapsed after the food was changed and before the period was commenced. The urine and stools were collected in the manner described by one of us,[11] and it was frequently noted that the baby was perfectly comfortable during the periods of investigation. Figure 1 shows that during the entire period the baby was in the hospital he gained from 4,280 gm., his weight on entrance, to 5,275 gm., his weight on discharge, June 16.

The periods were arranged so far as possible so that he would receive the same number of calories per kilogram of body weight per day. The amount of protein was increased in each successive period so that during the last period he was offered over three times as much as he had during the first period. During the last period the baby refused to take all the food offered him, thus reducing the protein intake. The milk used in mixing the formulas was raw. The writers believe that boiling the milk might have modified the results obtained.

TABLE 1.—TOTAL FIGURES FOR EACH THREE-DAY—

Period	Age, Mo.	Weight		Food							Urine	
		Start, Kg.	End, Kg.	Calories per 24 Hr.	Calories per Kg.	Fat, Gm.	Sugar, Gm.	Protein, Gm.	Nitrogen, Gm.	Ash, Gm.	Nitrogen, Gm.	Ash, Gm.
1	5¼	4.3	4.335	527	122	106	143	31	4.79	9.26	2.876	2.37
2	5¾	4.415	4.65	650	143	107	196	60	9.31	11.33	5.816	5.02
3	6	4.66	4.936	626	130	102	176	70	11.06	18.3	7.482	6.69
4	6½	4.93	5.17	649	130	84	217	89	13.91	21.6	8.065	7.4
5	6¾	5.06	5.235	628	123	64	233	109	17.01	27.66	11.893	13.87

Table 1 shows the total amount of calories, fat, sugar, protein, nitrogen and ash ingested for each period of three days, and the amount excreted in the urine and stools.

It was found that in Period 1 the baby was hungry, even though he was receiving 122 calories per kilogram of body weight. The investigations of Benedict and Talbot[12] have shown that the more a baby is underweight the greater will its basal heat production be per kilogram of body weight per twenty-four hours. It is not surprising then that it was necessary to give the baby more than 120 calories because he weighed less than the average weight for his age (4,300 gm. against the average weight of 6,800 gm.). The amount of food, therefore, was increased until the baby was satisfied in the second period. From this time on he received approximately the same total number of

11. Talbot: Apparatus for Metabolism Experiments in Male Infants, Jour. Am. Med. Assn., 1909, liii, 1818.

12. Morse and Talbot: Discussion of Benedict and Talbot, Dis. Nutrition and Infant Feeding, New York, 1915, p. 56.

calories in twenty-four hours. The calories per kilogram of body weight gradually fell as his weight increased, and it was necessary to vary the fat and sugar (lactose) in order to compensate for the increasing amount of protein given. Since the ash is principally in the protein of the milk, the ash increased as the protein increased.

Folin's[13] investigations on the adult showed that if a man ingested a diet containing a medium amount of protein, and again one nearly free from protein, the difference in amount of total nitrogen in the urine in the two instances was due almost exclusively to a difference in the output of urea. The quantity of creatinin eliminated remains independent of the quantity of protein metabolized, provided the diet is practitically creatin free, as Folin's were, the protein being supplied from milk. The same is less strikingly true of uric acid. This led Folin to distinguish between an endogenous, or repair, protein metabol-

—Period; Detailed Analysis of Urine Not Included

Stool								Nitrogen Balance, Gm.	Fat Utilized, per Cent.	Ash Balance, Gm.	Weight Balance, Gm.
Nitrogen,	Ash, Gm.	Total Fat, Gm.	Neutral Fat, Gm.	Fatty Acids and Soaps, Gm.	NH_3 Nitrogen, Gm.	NH_3 Nitro. in % Total N	Titrable Acid, Gm.				
0.895	4.21	19.16	0	19.16	0.087	9.7	51	1.02+	82	2.68+	35+
1.28	7.4	12.1	0.32	11.78	0.16	12.5	82	2.21+	89	1.09—	235+
1.475	7.84	8.42	0	8.52	0.12	8.1	42	2.10+	91	2.76+	276+
1.92	8.53	14.9	1.34	13.56	0.183	6.4	96	3.92+	88	5.67+	240+
3.477	12.08	12.37	1.03	11.34	0.254	7.3	194	1.64+	81	1.71+	180+

ism, and an exogenous, or energy, protein metabolism. That is, the term "endogenous" metabolism is used for the chemical processes which are concerned in maintaining the chemical structure of the cell protoplasm, in contrast to the processes of combustion, which the cell carries on for the purpose of using the resulting energy in accomplishing its physiologic functions. Creatinin and uric acid are regarded as being produced solely by endogenous metabolism. Probably some ammonia and urea are also produced by the processes of repair metabolism, but in the main ammonia and urea together represent the extent of the combustion of protein, for the sake of its energy content, and will depend on the amount left over after the cell protoplasm has supplied its structural needs. The absolute amount of ammonia appearing in the urine, is, as shown by Henderson and Palmer,[14] a measure of the extent to which this organic base is being used to maintain the nor-

13. Folin: Am. Jour. Physiol., 1905, xiii, 117.
14. Henderson and Palmer: Jour. Biol. Chem., 1914, xvii, 305.

mal reaction of the blood. The ammonia is available for this purpose at the expense of the neutral substance, urea.

If Folin's views are accepted, we may expect that since the process of cell repair probably goes on at a fairly constant pace in a normal

TABLE 2.—Day to Day Determinations for Acid Factors, Nitrogen—Three-Day Periods with—

Period	Protein in Food, Gm.	24-Hour Amount Urine, C.c.	Acid Excretion					Nitrogen, Mg.		
			+ (H)	Titrable Acid, C.c., N/10	NH_3 C.c., N/10	Total Acid, C.c., N/10	A/NH_3	Total Nitrogen	Urea N	NH_3 N
1	10.5	720	5.9	54	127	181	0.43	966	669	178
	9.9	815	5.3	84	170	254	0.5	966	624	238
	10.2	750	6	60	121	181	0.5	944	688	170
2	20.7	740	5.9	57	114	171	0.5	2,062	1,717	159
	19.1	775	6.4	55	116	171	0.47	1,842	1,614	163
	19.5	900	5.9	52	105	157	0.5	1,912	1,548	147
3	24.5	840	6.7	48	107	155	0.45	2,632	2,234	148
	24.6	760	6.7	48	131	179	0.37	2,470	2,039	183
	21.3	740	6.2	63	139	202	0.45	2,380	1,944	194
4	29.1	600	...	..	...	...	....	2,205	.....	...
	28.1	790	...	..	...	...	....	3,000	.....	...
	31.4	805	...	..	...	...	....	2,860	.....	...
5	35.8	850	...	..	...	...	....	3,871	.....	...
	35.3	700	...	..	...	...	....	3,942	.....	...
	37.4	900	...	..	...	...	....	4,080	.....	...

TABLE 3.—Summary from Table 2; Figures Are for—Results for the Three—

Period	Protein in Food, Gm.	Amount Urine, C.c.	Acid Excretion					Nitrogen, Mg.		
			+ (H)	Titrable Acid, C.c., N/10	NH_3 C.c., N/10	Total Acid, C.c., N/10	A/NH_3	Total Nitrogen	Urea N	NH_3 N
1	10.2	762	5.8	66	139	205	0.47	959	660	195
2	20.0	805	6.1	55	112	166	0.49	1,939	1,626	156
3	23.3	780	6.5	53	126	179	0.42	2,494	2,072	175
4	29.5	732	...	..	...	...	....	2,688	.....	...
5	36.2	817	...	..	...	...	....	3,964	.....	...

individual, the end products of endogenous metabolism will be constant in the absolute amount and unaffected by the varying amount of protein in the diet, whereas, the total urea plus ammonia nitrogen will vary directly with the protein intake. As there is no known organ in

the body in which protein is stored, the surplus protein (after cell repair and growth in infants have been supplied) must be burned.

Table 1 shows the total figures for each three-day period. During each period the baby gained rapidly in weight with the exception of

—AND SULPHUR PARTITION, PHOSPHATES AND CHLORIDS IN URINE FOR FIVE —INCREASING PROTEIN INTAKE

Nitrogen, Mg.					Sulphur, Mg. SO_3				Phosphates, Mg. P_2O_5	Chlorids, Mg.
Creatinin N	Creatin N	Uric Acid N	Undetermined N	Per Cent. of Food N in Urine	Total	Inorganic	Ethereal	Neutral		
25	1	52	61	59	174	95	29	50	360	350
25	3	31	41	62	200	121	..	44	540	770
19	4	33	30	59	202	118	26	58	500	90
20	13	11	150	64	363	269	14	81	520	520
19	11	10	25	61	338	246	18	73	550	570
20	11	13	173	62	317	239	12	67	420	560
22	28	19	181	64	429	362	14	54	550	600
21	29	17	181	59	433	361	16	57	540	830
22	22	17	191	66	420	366	10	45	600	1,130
20	25	..	...	48	385	318	13	54	660	690
22	28	..	...	68	509	423	17	69	730	1,680
20	22	..	...	58	501	421	15	65	720	1,340
25	39	..	...	69	672	594	12	65	940	1,800
22	40	..	...	71	679	588	20	71	920	1,800
23	39	..	...	70	680	595	22	70	950	1,800

—TWENTY-FOUR HOUR AMOUNTS OBTAINED BY AVERAGING THE —SUCCESSIVE DAYS OF EACH PERIOD

Nitrogen, Mg.				Sulphur, Mg. SO_3				Phosphates, Mg. P_2O_5	Chlorids, Mg.
Creatinin N	Creatin N	Uric Acid N	Undetermined N	Total	Inorganic	Ethereal	Neutral		
23	3	32	44	190	111	28	51	467	403
20	12	11	116	344	255	15	74	497	550
22	26	18	184	428	363	13	52	563	853
21	25	..	...	465	387	15	63	703	1,237
23	39	..	...	679	592	18	69	937	1,800

Period 1, in which he received the minimum amount of protein and fewer calories than during any other period. He was hungry after each feeding, and, therefore, the amount of food was increased until he was satisfied. During the remaining periods he was satisfied and

happy. The increase of nitrogen in the food was accompanied by a regular increase of the total nitrogen in the urine. This corresponds with the findings both in the infant and in the adult. There was an increase of ash in both the urine and the stools as the protein or nitrogen in the food was increased, and there was more ash in the stool than in the urine in all periods except Period 5, in which slightly more was excreted through the urinary tract than through the gastro-intestinal tract. The increasing amount of ash in the food did not affect its mode of exit from the body. There was, however, a marked increase in the titrable acidity of the stools in the last period, and a larger amount of sugar in the food during this period, which may have had some causative relation to these findings.

TABLE 4.—AMOUNT OF ETHEREAL SULPHATES IN URINE WITH AN INCREASING AMOUNT OF AMMONIA IN THE STOOL; FIGURES ARE FOR TWENTY-FOUR-HOUR AMOUNTS

Period	Protein per Kg. in Food, Gm.	NH_3 N in Stool, Gm.	Total Sulphur in Urine, Mg. SO_3	Ethereal Sulphates, Mg. SO_3		
				Total	Per Kg.	Percentage Total Sulphur
1	2.3	29	190	28	6.5	14.7
2	4.4	53	344	15	3.3	4.4
3	4.8	40	428	13	2.7	3
4	5.9	61	465	15	3.0	3.2
5	7.1	85	679	18	3.6	2.6

The retention of nitrogen (nitrogen balance) increased with the increase of nitrogen in the food up to the last period, when the baby refused to take all the food that was offered him, and, clinically, seemed to be on the verge of a digestive upset. In this period there was a marked diminution of the retention of nitrogen and a great increase in the nitrogen in the stools. During the last two periods there were casein curds in the stools, a very few in the fourth period, when there was a slight increase in the stool nitrogen, and many in the fifth period, when there was a great increase in the stool nitrogen. In the latter instance they made up 15 per cent. of the total fecal nitrogen.[15] Coincidently there was a decrease in the retention of ash. (We are unable to explain the negative ash balance in Period 2.) These figures make one speculate as to what might have happened if a further increase of protein had been persisted in. The

15. The stools during the other periods were remarkably uniform in quality. They were light yellow or yellow, of smooth salve-like consistency, never stiff. They were normal in all respects except that they were quite a bit larger than the usual twenty-four hour stool.

figures of the utilization of fat do not indicate that the fat digestion was influenced to any great degree by the changes made in the food.

Table 2 shows the day to day determinations for acid factors, nitrogen and sulphur partition, phosphates and chlorids in the urine for each of the five three-day periods.

Table 3, which is a summary of Table 2, shows that the amount of ammonia excreted in the urine is closely in proportion to the titrable acid in the urine. Henderson and Palmer[14] find in adults with normal kidneys that titrable acidity divided by the ammonia gives a fairly constant ratio of 0.75 in average, regardless of the amount of protein in the diet. The ratio titrable acidity divided by the ammonia in our

TABLE 5.—CREATININ, URIC ACID, ETHEREAL SULPHATES AND NEUTRAL SULPHUR PER KILOGRAM BODY WEIGHT WITH INCREASING PROTEIN INTAKE; FIGURES FOR TWENTY-FOUR-HOUR AMOUNTS

Protein per Kg. in Food, Gm.	Creatinin N per Kg., Mg.	Uric Acid N per Kg., Mg.	Ethereal Sulphates per Kg., Mg. SO_3	Neutral Sulphur per Kg., Mg. SO_3
2.3	5.3	7.4	6.5	11.8
4.4	4.4	2.4	8.3	16.3
4.8	4.6	3.8	2.7	10.8
5.9	4.2	...	3.0	12.5
7.1	4.5	...	3.6	13.4

first three periods was 0.47, 0.49, and 0.42. One of us, Gamble,[16] found in an investigation carried on at the Boston Floating Hospital that when more than the usual amount of protein was given the A/NH_3 ratio fell, in other words, increasing the protein in the diet resulted in an increase of urinary ammonia out of proportion to its usual relation to the amount of titrable acid. We regret that the acid factors were not determined during the last two periods.

The ammonia coefficient, that is, ammonia nitrogen divided by the total nitrogen for the first three periods, were 20 per cent., 8 per cent., and 7 per cent. The coefficient of 20 per cent. for the first period is very high and might be taken to mean an excess of acid excretion. This, however, is not the case, as is shown by the absolute values for ammonia and titrable acidity, which are practically the same in all three periods. The seemingly high coefficient is due to a low total nitrogen in the urine, because of the low protein intake. Since a high ammonia coefficient is generally taken as evidence of acidosis, it is important to bear in mind that when the food contains only a small

16. Gamble: Not yet published.

amount of protein, a high ammonia coefficient will not necessarily mean acidosis. If, on the other hand, there is an average amount of protein in the diet, a high ammonia coefficient is of greater significance.

The urea nitrogen increased regularly with the amount of nitrogen in the food, as it does in adults, and indicates the extent of the exogenous protein metabolism.

The creatinin in the urine remained extremely constant in the total amount, and independent of the quantity of protein metabolized. It measures the endogenous metabolism of the individual. Previous investigators have found that the excretion of creatin in the urine of man is independent of the amount of protein in the food.

Our figures show that the amount of creatin in the urine of this infant depended on the amount of protein in the food. It increased

TABLE 6.—SUMMARY OF ENERGY—

Date	Body Weight and Surface	Height, Cm.	Age, Mo.	Carbon Dioxid per Hour, Gm.	Respiratory Quotient
5/21/14	4.74 Kg.	60	5½	6.48	....
	$10.3\sqrt[3]{w^2} = 0.291$ Sq. M.			5.02	0.88
				6.04	....
5/23/14	4.75 Kg.	60	...	7.94	....
	$10.3\sqrt[3]{w^2} = 0.291$ Sq. M.			4.72	0.84
				6.53	....
6/ 9/14	5.12 Kg.	62	6	7.6	....
	$10.3\sqrt[3]{w^2} = 0.306$ Sq. M.			5.9	0.92

* Periods were of least activity according to the kymograph records.

with the protein as did the urea. It seems likely, therefore, that the creatin in the urine of this infant was a product of his exogenous metabolism.

The uric acid was highest with the lowest protein intake.

The ethereal sulphates, according to Folin, are almost entirely the product of endogenous metabolism. Table 3 shows that in our baby the ethereal sulphates were unaffected by the increase of protein in the food. The inorganic sulphates increased regularly with the increase of protein in the food and are, like urea, a product of exogenous metabolism. The neutral sulphur is, however, roughly constant.

Table 4 shows the amount of ammonia in the stools, which may be taken as an index of intestinal putrefaction. It increased with the increasing protein intake. This substantiates other findings of

Gamble,[17] but does not show any relation between the ethereal sulphates of the urine, which remain absolutely constant, and the stool ammonia. The distinctly larger amount of ethereal sulphates, both total and per kilogram of body weight, in the period with the least ammonia in the stools seems to indicate that indol, phenol, and skatol in the intestinal canal do not contribute much to their formation.

The phosphates and chlorids in the urine increased with the increasing food protein in all five periods, while the undetermined nitrogen increased in like manner in the first three periods (the last two were not determined). It is possible that the undetermined nitrogen contains other products of the exogenous metabolism.

In Table 5 creatinin, uric acid, and the ethereal sulphates, products of the endogenous metabolism, are put on the per kilogram basis

—METABOLISM OF A BOY, F. W. L.

Heat Produced per 24 Hours, Calories		Rectal Temperature	Average Pulse Rate	Remarks
Per Kg.	Per Sq. Meter (Lissauer)	C. F.		
..	.....	36.8 (98.2)	127	Formula feeding (6 oz.) about ½ hour before the observation was started
72	1,175*	.....	118	
87	1,412	36.8 (98.2)	127	
..	.....	37.3 (99.2)	138	Formula feeding (5 oz.) about ½ hour before the observation was started
70	1,144*	.....	117	
97	1,584	37.0 (98.6)	130	
..	.....	36.9 (98.4)	142	Formula feeding (6 oz.) about 1 hour before the observation was started
76	1,268*	37.1 (98.8)	137	

because it seems likely that the endogenous metabolism depends on the protoplasmic mass of the individual infant, just as does the total energy metabolism. The interesting point brought out in this table is that whereas the figures remain relatively constant during the last four periods, in the first period in which the protein approaches the minimum protein intake necessary for a nitrogenous equilibrium, there is a definite increase in the excretion of these three bodies, even though there was a small positive nitrogen balance in this period. Can it mean that the level of endogenous metabolism rises as the minimum protein intake necessary for a nitrogenous equilibrium is approached?

17. Gamble: Ammonia and Urea Content of Infants' Stools, AM. JOUR. DIS. CHILD., 1915, ix, 519.

The basal energy metabolism[18] was investigated between Periods 1 and 2, but no periods which could be considered quiet periods were obtained. Between Periods 2 and 3 two separate quiet periods were obtained, and between Periods 4 and 5 one quiet period was obtained. These periods are herewith recorded. Although the small number of periods does not justify any conclusions, it can be seen that the calories per square meter are distinctly higher with the higher protein intake than with the lower protein intake. These findings are, therefore, constant with those publishel from Lusk's laboratory.

SUMMARY

This work shows that the metabolism of F. W. L. was going on in a normal manner despite the increase of protein in the food. The baby gained weight very rapidly after he received sufficient calories to satisfy his appetite. Since he was considerably below the average weight for the age when the work commenced and gained so much weight during the investigations, the question may be brought up as to whether he falls into a similar class to that occupied by a patient convalescing from typhoid fever. It is impossible to answer this, but clinically he came into the class of babies "doing well."

The level of his metabolism varied because he needed more calories in the beginning, when he was underweight, than at the end, when he more nearly approached the normal weight for his age. During the last period he did not take all the food that was offered him, his natural instincts and appetite protecting him from a food that was ill balanced. This experience makes us speculate as to whether other investigators may not have had the same experience, and, for that reason, found no chemical evidence of a protein disturbance of metabolism. The endogenous metabolism of uric acid, creatinin and ethereal sulphates was maintained on a very constant level, while the exogenous metabolism, namely, urea, creatin, inorganic sulphates and the metabolism of phosphates, chlorids and undetermined nitrogen, increased with the protein in the food. The fat and carbohydrate absorption was within normal limits, although the fat utilization in Periods 1 and 5 was almost outside normal limits. The retention of nitrogen suddenly dropped in the last period, even though there was a greater intake and absorption of nitrogen. This loss was found in the stools, in which casein curds were found in large numbers. The ammonia in the stools increased with the increasing protein intake, and may be considered an index of intestinal putrefaction.

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18. The work was done with the apparatus of the nutrition laboratory of the Carnegie Institution of Washington.

THE BACTERIOLOGY OF THE URINE IN HEALTHY CHILDREN AND THOSE SUFFERING FROM EXTRA-URINARY INFECTIONS*

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The problem of pyelocystitis in infancy and childhood has become more and more important as our knowledge of the frequency of the infection has increased, and the possible serious consequences that it may entail. A few facts regarding pyelocystitis have been pretty well established, namely, that the infection is very much more common in girls than in boys, that the infecting organism is most frequently the *Bacillus coli,* and that the symptomatology of the condition is so indefinite as to make a diagnosis practically entirely dependent on the examination of the urine.

Regarding the mode of infection there seems to be considerable difference of opinion. In practically all articles on the subject, three possible modes of infection are given, namely, (1) ascending infection in the lumen of the urethra; (2) infection by way of the anastomosing lymphatics of large intestines and urinary tract; (3) infection by way of blood stream.

Regarding the third type of infection, the pathologic anatomy of the kidney proves that this type of infection does occur. In like manner the lymphatic route is quite definitely proved. The consensus of opinion in pediatric literature appears to be, however, that the infection by way of the lumen of the urethra is the commonest. The main facts in favor of the urethral route are the predominance of cases in girls, the shortness of the urethra, and the fact that the orifice of the urethra is constantly contaminated with colon bacilli.

Although it may appear that these three facts speak in favor of an ascending infection by way of the lumen of the urethra, nevertheless the question is far from being definitely settled.

In order to get a basis for future work it seemed essential first of all to determine the bacteriology of the normal urine and urethra. It is the object of this paper to record the bacteriologic findings of catheterized specimens of urine taken from thirty girl infants and from thirty-one girls over 2 years of age.

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* Submitted for publication June 14, 1916.
* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

In an examination of the literature on urinary findings in health practically only a single paper, by Ross,[1] has been found. Ross catheterized nineteen normal children (age not given); of these nineteen specimens, eleven were sterile and eight showed a staphylococcus; of the eight, only three showed staphylococci in the second portion of the urine. Besides these, he catheterized eighty-seven girls the specimens from none of whom were sterile. These contained in forty-three instances pure cultures of colon bacilli, in nineteen the *Bacillus proteus*, and in twenty-five instances a staphylococcus. It was impossible for us to tell from the text how these cases are to me classified, as only three of the colon group did he classify as evident pyelitis and only one in the proteus group. Of the staphylococcus he says, "there is no reason to attach importance to their presence." There are several criticisms to be made of this paper: first, that the urine was incubated for twenty-four hours in liquid mediums and then plated, and second, that the plates were incubated for only forty-eight to seventy-two hours. Under the first point it can be said that one type of organism may easily overgrow other organisms present so as to appear to be present in pure culture, and by the second method of treatment one gets no idea whatsoever as to how many organisms per cubic centimeter there are present in the urine, and it can also be said that many specimens will be sterile at the end of forty-eight to seventy-two hours and yet show a number of colonies at the end of a week.

The technic we employed in obtaining the specimens was as follows: The patient was placed on a table with the limbs widely spread apart, so that the orifice of the urethra was plainly visible. A sterile cotton applicator was now used to thoroughly cleanse the vagina, the external genitalia not being cleansed, while an assistant kept a constant fine stream of 1 per cent. lysol solution playing on the part. The region about the urethral orifice was naturally given special attention. Then with a dry sterile applicator the orifice of the urethra was mopped dry. A sterile catheter was now carefully introduced without touching anything but the orifice. In the infant there is usually a small fold of mucous membrane lying over and covering the urethral orifice, which unquestionably protects the urethra from gross fecal contamination, but makes it almost impossible to avoid touching when introducing the catheter. If by any chance a portion of the vagina other than the orifice was touched a fresh catheter was taken. The urinary samples were collected in two or three sterile tubes, the flow of urine being controlled by compressing a piece of rubber tubing about 2 inches long that was attached to the glass catheter. These samples were labeled

1. Ross: Bacteriology of the Urinary Tract in Children, Lancet, London, 1915, i, 484.

1, 2, and 3, and were cultured separately so as to determine the difference between the first and last urine passed.

One cubic centimeter of urine was used in making the litmus-lactose-agar plates and blood-agar plates, 2 c.c. of urine in the deep dextrose-agar and deep blood-agar tubes. This variety of medium makes identification of the colon group easy, shows the organisms growing only on blood medium, and the deep tubes give opportunity for anaerobic growth. In the course of a few experiments Tubes 2 and 3 were found to be practically identical, so that in the majority of the cultures taken only 1 and 2 were used. Tube 1 was grown in deep dextrose-agar tubes and on a litmus-lactose plate. Tube 2 was grown on a litmus-lactose plate, a blood-agar plate, and in a deep blood-agar tube. In the passage of the catheter through the urethra a certain number of bacteria are carried into the bladder and are washed into the first portion of the urine; so that Specimen 1 represents urethral as well as bladder flora. In order to compare the first and last portion of the urine we have charted the cases as follows designating the first portion as No. 1 and the last as No. 2.

The analysis of Table 2 shows the following:

The chemical and microscopic examination of the urine of the normal cases showed in no instances albumin, the specimens were all acid, a few of them cloudy with urates and phosphates. In a single instance there were a few leukocytes found, in three instances epithelial cells, and in no instance any casts.

Of the twelve normal cases five had sterile urine; of the remaining seven, two had organisms in the first portion of the urine, but none in the second. In one instance No. 1 was sterile when No. 2 contained 2 bacteria per cubic centimeter. In only one instance was a colon-like organism found in this entire series. A single colony of the *Bacillus alkaligenes* developed from 1 c.c. of the first portion of urine in Case 3. Of the remaining five specimens of No. 1 that were not sterile, three showed 1 organism per cubic centimeter and two, 3 organisms per cubic centimeter. No. 2 contained 1 organism per cubic centimeter four times and 2 organisms once. In every instance in which more than 1 organism per cubic centimeter was found there were two types of organism identified.

The examination of the urine of the patients with extra-urinary infections showed very frequently pathologic constituents. The urine was alkaline three times, acid fifteen times. Albumin was present three times. On microscopic examination casts were present three times, a few leukocytes nine times, many leukocytes two times, and red blood corpuscles twice. The two specimens in which many leukocytes and red cells were found contained also a large number of casts, in fact formed a sediment that filled the bottom of the tube for about

one-half inch. A diagnosis of pyelocystitis was made from the microscopic examination of the urine, but cultures did not bear out this finding. The infants were both very acutely ill, and the urine was highly concentrated. This finding emphasized the necessity of care in making a diagnosis of pyelocystitis from a single specimen, even when it is obtained by catheterization.

In Table 3, eighteen cases of extra-urinary infections, there were five instances in which the specimens were sterile. Of the remaining thirteen cases No. 1 was sterile once; in two instances there were 1 or 2 bacteria per cubic centimeter, in two instances from 3 to 5 per cubic centimeter, in two instances from 6 to 10 per cubic centimeter, in four instances from 11 to 20 per cubic centimeter, and in three instances from 21 to 50 per cubic centimeter. In like manner in No. 2 in five instances there was 1 bacterium per cubic centimeter, and in five instances there were from 2 to 5 per cubic centimeter, in one instance 7 per cubic centimeter, and in one instance 13 per cubic centimeter.

An analysis of the six cases in which colonlike organisms were found is shown in Table 1.

TABLE 1.—Analysis of Cases in Table 3 Showing Colonlike Bacilli

Case Number	No. 1		No. 2	
	Organisms per C.c.	Gram-Negative Bacilli per C.c.	Organisms per C.c.	Gram-Negative Bacilli per C.c.
13	20	10	1	1
15	6	3	4	2
19	20	10	4	0
24	50+	3	13	0
27	4	2	2	1
29	20	15	4	0

In their relation to the problem of cystitis this group of cases is perhaps the most interesting. Of eighteen cases, six showed the presence of gram-negative bacilli in the first specimens and in one-half of these in the second specimen also. In the second specimen in two instances there was a single organism per cubic centimeter, and in the third, 2 organisms. In each instance the flora of the second represents a dilution of the first, and in all probability represents urethral organisms.

The urines that showed gram-negative bacilli in both No. 1 and No. 2 were from (1) a case of severe atrophy with marked retention of urine, 75 c.c. being obtained on catheterization, the catheter being passed while urine was flowing, No. 1 showing *B. coli* and gram-positive staphylococcus, and No. 2 showing a single colony of *B. coli;*

(2) a case of bronchitis which had in Nos. 1 and 2 *B. enteritidis* and a gram-positive staphylococcus; (3) a case of pneumonia which had in No. 1 and No. 2 a gram-positive staphylococcus and *B. coli.*

Cases 4 and 5 of this series are especially interesting because the catheterized urine in both instances was loaded with pus cells and casts and gave a positive test for albumin, and yet No. 2 in one instance contained only 13 gram-positive staphylococci per cubic centimeter and the other 2 staphylococci and 2 colon bacilli per cubic centimeter. The first of those catheterized at a later date gave a sterile urine, no treatment having been instituted in the meantime. When one considers that in cases of cystitis the urine diluted 1 to 100 million or even 1 to 1 billion usually shows innumerable colonies, the importance of the finding of a single organism per cubic centimeter of undiluted urine is not to be overestimated.

To pass on to the analysis of Tables 3 and 4, it is seen that the normal patients over 2 years of age resemble those below 2 very much in the absence of finding on microscopic and chemical examination. In four cases there were a few leukocytes present and in one instance a positive test for albumin.

In the cases of extra-urinary infections there were only three that showed a positive test for albumin, five with small numbers of leukocytes, one with numerous leukocytes (present in uncentrifuged specimen) and in four instances hyaline casts.

Of the specimens taken from girls above 2 years we find that the number of times sterile urine was obtained in both No. 1 and No. 2 was almost the same as in series 1. In thirteen cases out of thirty-one all cultures remained sterile. The number of bacteria per cubic centimeter in the different urines that showed organisms was very much smaller, however; in only one specimen were there more than five organisms per cubic centimeter. This urine contained twenty-one organisms per cubic centimeter of a long-chained, nonhemolytic streptococcus in pure culture. In only two instances was a gram-negative bacillus found, in both instances the bacillus proteus. In two instances a single colony of the hay bacillus was found. All the remainder were either gram-positive cocci or diphtheroid bacilli. Of the eighteen cases that showed growth in No. 1 or No. 2, in four No. 1 showed no growth; in nine No. 1 showed 1 organism per cubic centimeter; in five No. 1 showed from 2 to 5 organisms per cubic centimeter.

In the eighteen cases No. 2 showed in seven cases no growth; in three cases 1 organism per cubic centimeter; in four cases 2 organisms per cubic centimeter; in one case 4 organisms per cubic centimeter; in one case 21 organisms per cubic centimeter (blood plate).

In this group of thirty-one cases there are only two specimens of urine that contained gram-negative bacilli. These two cases were both

TABLE 2.—Urinary Findings in Normal—

Case	Age, Mo.	Diagnosis	Examination of Urine					
			Reaction	Turbidity	Albumin	Cells	Casts	Bacteria
1	12	Normal	Acid	0	0	Few	0	0
2	7	Normal	Acid	0	0	Few	0	0
3	24	Normal	Acid	Phosphates	0	0	0	0
4	5	Normal	Acid	0	0	Few	0	0
5	11	Normal	Acid	Urates and phosphates	0	Epithelial cells; few leukocytes	0	0
6	9	Normal	Acid	0	0	0	0	0
7	8	Normal	Acid	0	0	Few	0	0
8	14	Normal	Acid	+	0	0	0	0
9	6	Normal	Acid	Amorphous yellow precipitate	0	0	0	0
10	14	Normal	Acid	0	0	0	0	0
11	12	Normal	Acid	+	0	0	0	0
12	13	Normal	Acid	0	0	0	0	0

TABLE 3.—Urinary Findings in Cases of Extra-Urinary—

Case	Age, Mo.	Diagnosis	Examination of Urine					
			Reaction	Turbidity	Albumin	Cells	Casts	Bacteria
13	8	Atrophy	Acid	Slight	Trace	0	+	0
14	12	Acute rhinitis	Acid	0	0	Few pus cells	0	0
15	14	Bronchitis	Acid	0	0	0	0	0
16	9	Bronchopneumonia	Acid	0	0	Few pus and epithelial cells	0	0
17	6	Exudative diathesis	Acid	+	0	Pus and epithelial cells	0	0
18	4	Exudative diathesis	Alkaline	0	0	0	0	0
19	8	Exudative diathesis	Acid	0	0	Few mononuclears	0	0
20	12	Exudative diathesis; tetany	Acid	0	0	0	0	0
21	13	Healing gland of neck	Acid	0	0	0	0	0
22	15	Healing gland of neck	Acid	0	0	0	0	0
23	10	Healing gland of neck	Alkaline	0	0	+	Few granular	0
24	11	Nephritis	Acid	+	+	Many R.B.C.; few W.B.C.	0	0
25	11	Nephritis	Acid	0	0	Few pus cells	0	0
26	18	Pneumonia	Alkaline	0	0	Few mononuclears	0	0
27	10	Pneumonia	Acid	++	+	R.B.C. +; pus ++	+	0
28	9	Rhinitis	Acid	Slight	0	Few round and epithelial cells	0	0
29	6	Tetany	Acid	0	0	0	0	0
30	6	Whooping cough	Alkaline	0	0	Few	0	0

—Cases of Patients Under Two Years of Age

Culture No. 1			Culture No. 2		
Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism	Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism
1	0	Gram-positive coccus	1	0	Gram-positive coccus
0	0	0	2	0	Gram-positive coccus; pseudo-diphtheroid
1	1	Bacillus alkaligenes	1	0	Gram-positive coccus
3	0	Hay bacillus; gram-negative bacillus in chains	1	0	Hay bacillus
3	0	Gram-positive coccus; pseudo-diphtheroid	1	0	Gram-positive diplococcus bacillus
1	0	Gram-positive coccus	0	0	0
1	0	Gram-positive coccus	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0

—Infections in Patients Under Two Years of Age

Culture No. 1			Culture No. 2		
Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism	Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism
22	10	B. coli communis; gram-positive coccus	1	1	B. coli communis
0	0	0	0	0	0
6	3	Gram-positive coccus; B. enterid.	4	2	Gram-pos. coccus; B. enterid.
5	0	Gram-positive coccus	4	0	Gram-positive coccus
22	0	Gram-positive coccus; pseudo-diphtheroid	7	0	Gram-positive coccus; pseudo-diphtheroid
0	0	0	*		
20	10	Gram-positive coccus; gram-negative bacillus	4	0	Gram-positive coccus
0	0	0	0	0	0
12	0	Gram-positive coccus; gas-forming anaerobe	1	0	Gram-positive coccus
6	0	Gram-positive coccus	1	0	Hay bacillus
0	0	0	1	0	Pseudodiptheroid
50+	3	Gram-positive coccus; pseudo-diphtheroid; gram — bacillus	13	0	Gram-positive coccus
0	0	0	0	0	0
1	0	Gram-positive coccus	*		
4	2	Gram-positive coccus; B. coli communis	2	1	Gram-positive coccus; B. coli communis
2	0	Gram-positive coccus; gram-negative bacillus (anaerobe)	1	0	Gram-positive coccus
20	15	B. coli; gram-positive coccus; hay bacillus	4	0	Gram-positive coccus
0	0	0	0	0	0

* For Nos. 18 and 26 only one sample was obtain ed.

TABLE 4.—URINARY FINDINGS IN—

Case	Age, Yrs.	Diagnosis	Examination of Urine				
			Reaction	Albumin	Cells	Casts	Bacteria
1	4	Normal	Acid	0	0	0	0
2	4	Normal	Acid	0	0	0	0
3	5	Normal	Acid	0	0	0	0
4	3	Normal	Neutral	0	0	0	0
5	5	Normal	Acid	0	0	0	0
6	6	Normal	Acid	0	0	0	0
7	5	Normal	Acid	0	Few mononuclears	0	0
8	5	Normal	Acid	+	0	0	0
9	5	Normal	Acid	0	Few round cells	0	0
10	5	Normal	Acid	0	0	0	0
11	5	Normal	Acid	0	Few pus cells	0	0
12	6	Normal	Acid	0	0	0	0
13	3	Normal	Acid	0	0	0	0
14	3	Normal	Acid	0	0	0	0
15	3	Normal	Acid	0	0	0	0
16	3	Normal	Acid	0	0	0	0
17	5	Normal	Acid	0	Few mononuclears	0	0
18	3	Normal	Acid	0	0	0	0

TABLE 5.—URINARY FINDINGS IN CASES OF EXTRA-URINARY—

Case	Age, Yrs.	Diagnosis	Temperature	Examination of Urine				
				Reaction	Albumin	Cells	Casts	Bacteria
1	10	Chorea	0	Acid	0	Few	0	0
2	11	Chorea	0	Acid	0	One group	1 granular and 1 waxy	0
3	10	Chorea	0	Acid	0	+ mononuclear and polymorph.	0	0
4	3	Tetany	0	Acid	0	0	Few casts and cylinders	0
5	3	Pneumonia	0	Acid	0	Few	0	0
6	12	Pneumonia	102	Acid	+	Few	+	0
7	11	Chorea	0	Acid	0	Few squamous	0	0
8	10	Endocarditis	97	Acid	Trace	Few	Hyaline and waxy	0
9	6	Meningitis; bronchitis	100	Acid	0	0	Few hyaline and cylindrical	0
10	3	Suspected cystitis	*	Acid	0	0	0	0
11	9	No diagnosis	103	Acid	0	0	0	0
12	6	Rhinitis	102	Acid	0	Pus cells	0	0
13	6	Suspected cystitis	0	Acid	0	0	0	0

* Fever for two weeks at a previous time.

—Normal Girls Over Two Years of Age

Culture No. 1			Culture No. 2		
Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism	Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism
0	0	0	0	0	0
0	0	0	4	0	Pseudodiphtheroid
0	0	0	0	0	0
0	0	0	21	0	Streptococcus (long chain)
1	0	Gram-positive coccus (short chained)	0	0	0
2	0	Gram-positive diplococcus	2	0	Gram-positive diplococcus
1	0	Gram-positive coccus; hay bacillus	0	0	0
1	0	Gram-positive coccus	0	0	0
0	0	0	1	0	Gram-positive coccus
0	0	0	0	0	0
5	0	Pseudodiphtheroid; 1 gram-positive coccus; 1 mold	0	0	Pseudodiphtheroid; mold
0	0	0	0	0	0
0	0	0	2	0	1 mold; 1 short-chained coccus
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
1	0	Gram-positive coccus	0	0	0

—Infections in Patients Over Two Years Old

Culture No. 1			Culture No. 2		
Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism	Number Organisms per C.c.	Number Gram-Negative Bacteria per C.c.	Types of Organism
1	0	Gram-positive coccus	2	0	Gram-positive coccus
3	0	Gram-positive coccus	2	1	Gram-positive coccus; B. proteus vulgaris
0	0	0	0	0	0
0	0	0	1	1	B. proteus vulgaris
4	0	Gram-positive coccus			
1	0	Gram ± staphylococcus			
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
1	0	Gram-positive coccus	0	0	0
0	0	0	0	0	0
1	0	Hay bacillus	0	0	0
1	0	Gram-positive coccus	0	0	0

in the first group of cases catheterized. The only case in which there were more than 5 organisms per cubic centimeter was a case in which twenty-one colonies of streptococci grew out of the blood-agar plate. There was no growth on the litmus-lactose plates. The small number of organisms probably all represent bacteria washed in from the urethra. This series of cases consisted of thirteen hospital cases, two acutely ill, the remaining suffering from chronic infections, and eighteen normal children in an orphan asylum.

SUMMARY

In 118 specimens of carefully catheterized urine from sixty-one different girls, sixty-one were sterile and fifty-seven contained bacteria. Of those from normal infants, thirteen were sterile and eleven contained bacteria. Of those from extra-urinary infections in patients under 2 years of age, none were sterile and twenty-four contained organisms. In those from girls over 2 years, thirty-eight were sterile and twenty-two contained bacteria. The number of bacteria found in Series 1 was considerably larger than in Series 2. This may be explained by the fact that in the older children one can cleanse the urethral orifice much easier than in the infant and introduce the catheter directly into the urethra. The bacterial flora was practically the same in both series, gram-positive cocci and diphtheroid organism predominating, the former being present in practically every case in which any organisms were found. In no instance were gram-negative bacilli found in such numbers in both specimens that it seemed probable that it was more than an accidental contamination from the urethra.

CONCLUSIONS

1. Organisms of the colon bacillus group are not normal inhabitants of the female urethra.

2. In extra-urinary infections occurring in the first two years of life the colon group of bacilli are frequently found in the urethra (one-third of the cases).

3. In girls over 2 years of age the urine is almost free of organism, and in our series entirely free from bacilli of the colon group (eighteen normal, twelve other infections).

SYMPOSIUM ON SYPHILIS

FREQUENCY OF HEREDITARY SYPHILIS*

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Reliable statistics on the frequency of a given disease are dependent on two factors: study of large groups of individuals, accuracy of diagnosis. Students of such a problem may compile their statistics from critical analysis of the literature and from their own personal observations. In these personal observations accuracy of diagnosis can be obtained only by careful methods of investigation, both clinical and laboratory; the clinical including an inquiry into the family and personal history of the individual and the practice of making a physical examination; the laboratory including the usual routine tests and, in addition, any methods specially applicable to the subject under discussion.

In accordance with this general plan, we have made an inquiry as to the incidence of hereditary syphilis, drawing our final conclusions from an analysis of the literature and an intensive study on our own part of 695 patients at The Children's Memorial Hospital.

LITERATURE

Comparatively few large groups of cases of hereditary syphilis have been carefully studied by both clinical and laboratory investigations.

Epstein,[1] in a Prague foundling asylum, obtained positive Wassermann reaction in 33 per cent. of 236 newly born infants, and in 10 per cent. of their mothers.

Blackfan, Nicholson and White[2] found a positive Wassermann reaction in 2 per cent. of 101 hospital infants, that is, in two infants. One of these patients was without symptoms, but gave a complete reaction. The authors accept the specificity of a complete reaction, but consider

*Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

1. Davis, E. P.: Amer. Jour. Obst., 1916, lxxiii, 769.
2. Blackfan, Nicholson and White: AM. JOUR. DIS. CHILD., 1913, vi, 162.

the significance of a weak or partial serum reaction as still undetermined (1913).

Holt[3] obtained, in 178 hospital children, eleven positive Wassermann reactions, or 6 per cent.

Elliott[4] (Glasgow) obtained positive Wassermann reaction in 10.8 per cent. of 130 hospital children. He used the method recommended by Browning and Mackenzie, and also adopted the standards of those authors.

Browning[5] studied 3,000 cases of syphilis as a whole, quoting Watson as follows: Of 331 outpatient department children in Glasgow, forty-six, or 14 per cent., were syphilitic, 10 per cent. clinically and by Wassermann reaction, 4 per cent. clinically only. These patients were carefully studied, especially as to their family history; in all patients with a positive Wassermann reaction some other member of the family also gave a positive reaction.

Jeans and Butler[6] found in the outpatient department of a St. Louis hospital, among 5,185 new patients, 108 cases (2 per cent.) of hereditary syphilis. But dividing their patients into two groups, those under and those over 13 months of age, the proportion of syphilitics was 4.9 per cent. in the first or younger group, and 1.5 per cent. in the older group. The lower figure in the second group is due to the large number of deaths among syphilitics under 1 year of age. The proportion in the first group, 4.9 per cent., of course represents more correctly the proportion in this particular series.

There is no statement as to the number of Wassermann tests done.

A report[7] from a children's clinic in Prague states that of 2,533 infants, 5.7 per cent. were syphilitic, either clinically or by the Wassermann test.

Whitney[8] reports from the outpatient department of a San Francisco Hospital a series of 7,885 patients. There were 915 children, all studied clinically and by the Wassermann test, and 2.9 per cent. were syphilitic.

Of the above eight reports on the incidence of hereditary syphilis, seven are based on both clinical and laboratory (Wassermann) examinations and one apparently on serum tests alone. The four American estimates range from 2 to 6 per cent., the two European (Continental) are 3.3 and 5.7 per cent. The two estimates from Scotland, both from Glasgow, are the highest found, being 10.8 and 14 per cent.

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3. Holt: Am. Jour. Dis. Child., 1913, vi, 166.
4. Elliott: Glasgow Med. Jour., 1914, lxxxi, 339.
5. Browning: Brit. Med. Jour., 1914, 1, 77.
6. Jeans and Butler: Am. Jour. Dis. Child., 1914, viii, 327.
7. Steinert, E., and Flusser, E.: Arch. f. Kinderh., Nov. 2, 1915, Abst., Jour. Am. Med. Assn., 1916, lxvi, 608.
8. Whitney: Jour. Am. Med. Assn., 1915, lxv, 1986.

One of us (F. S. C.[9]) in 1912 reported a series of 102 infants and children, with thirty-nine positive Wassermann reactions, twenty-nine of which, on the combined basis of physical signs and positive reaction, were regarded as syphilis. In almost all of these cases the reaction was weakly positive, a single plus. In view of recent observations on the significance of an incomplete reaction, further discussion of that paper seems necessary.

During the last two or three years various workers have expressed the opinion that a Wassermann reaction variously described as a "single plus," "incomplete," "faintly" or "weakly" positive, is by no means diagnostic of syphilis, but is found in other conditions. Fordyce in 1914 said that a partial or transient complement fixation is sometimes seen in cachectic states, as well as in leprosy and yaws, and that an indeterminate or weakly positive reaction is of value as an indication for treatment, but of little diagnostic importance unless accompanied by other symptoms.

Nicholas and Gaté,[10] in 1914, working in a dermatologic clinic, report a positive Wassermann reaction in 39 per cent. of seventy-one nonsyphilitic patients, presenting a great variety of conditions, among others impetigo, eczema and pediculosis. They say nothing of the degree of intensity of the reaction in these cases, nor do they give their methods of performing the test. Their results in cases of undoubted syphilis, however, indicate that their technic and methods were reliable. It is possible that in the nonsyphilitic cases their reactions were +, weakly positive. We have ourselves, as described below, obtained such a reaction in cases of eczema.

Craig,[11] in 1915, classifies his reactions as + +, +, + —, and —. He interprets + + as syphilis, regardless of history or clinical signs, and + or + — as always doubtful unless the history and symptoms are well-defined.

Hesse[12] distinguishes two groups of nonsyphilitic disorders in which the Wassermann reaction is positive: (1) protozoa; (2) scarlatina, tuberculosis, malaria, pneumonia, lupus erythematosus, carcinoma and sarcoma. Here, again, we could confirm a weakly positive reaction in certain of these conditions, namely, tuberculosis and pneumonia.

Moore[13] eliminates a faintly positive reaction without clinical signs and urges a repetition of the test.

It thus becomes evident that too much reliance cannot be placed on an incomplete Wassermann reaction by itself. Either the reaction, if

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9. Churchill, F. S.: Am. Jour. Dis. Child., 1912, iii, 363.
10. Nicholas and Gaté: Bull. Soc. franç. de dermat. et de syph., 1914, xxv, 200.
11. Craig: Am. Jour. Med. Sc., 1915, cxlix, 41.
12. Hesse: Abstract, Am. Jour. Obst., May, 1916.
13. Moore: Jour. Am. Med. Assn., 1915, lxv, 1980.

taken by itself, must be strongly positive, or, if weakly positive, must be accompanied by well-defined family history or physical signs, to justify a diagnosis of syphilis. I have, therefore, reviewed my work of five years ago, applying to it our present standard, and find that only five of the original twenty-nine cases will stand the test, and that, therefore, only five of the 102 cases reported in 1912 can be regarded as syphilis, basing the diagnosis now on either a strongly positive Wassermann reaction alone, or on the combination of a weakly positive reaction and well-defined physical signs. This makes the incidence of syphilis in that series about 5 per cent.

The Authors' Present Cases

We have made an intensive study of 695 cases, unselected, in age from prematurity to 12 years, taken just as they entered the hospital, during the period from Nov. 1, 1915, to June 1, 1916. Of these, twenty-three, or 3.3 per cent., have been found to be cases of syphilis. We have excluded only the children admitted for the removal of tonsils and adenoids. These patients remain in the hospital only twenty-four hours, too short a period for thorough study.

In considering the diagnosis in these cases, due weight has been given to both clinical and laboratory investigations. In addition to the regular routine procedures observed with all cases on admission, special attention has been paid on the clinical side to the family history, to the presence or absence of characteristic physical signs, and on the laboratory side to the Wassermann and luetin tests, Wassermann tests having been performed on every patient, luetin tests on 171 patients. The significance of these various diagnostic methods must be briefly considered.

The clinical history and manifestations may be either suggestive or conclusive. Thus, a history of chancre in the father, of repeated miscarriages or stillbirths in the mother, obtained in the history of an emaciated infant, must be regarded as at least suggestive, even though the infant presents none of the characteristic lesions of syphilis; but if to such a family history be added the observation of one or more characteristic physical signs, such as an enlarged spleen or palpable epitrochlear glands, the diagnosis of syphilis is practically certain; finally, marked characteristic lesions in the infant, such as "snuffles," rhagades, signs about the buttocks or on the palms and soles, can leave no doubt of the nature of the condition, even though we have failed to elicit a specific family history.

The laboratory investigations also may be either suggestive or conclusive. As already stated, two special tests have been applied in this series, the Wassermann and luetin tests.

(A) WASSERMANN TEST

We have considered this test one of the most reliable single signs in diagnosis. In an account of a study of cases which involve the use of this reaction, it should be deemed necessary to give in detail a description of the methods employed in the performance of the tests, together with the values placed on the different varieties of results. Although there has been some tendency toward uniformity and standardization in the technic of the Wassermann test, there are still many variations in the hands of different workers, to some degree necessarily so, as there is still much to be done to improve the reaction. However, in analyzing reports of Wassermann tests, it is important to know not only that results were either positive or negative, but also to know how the tests were made and interpreted. Otherwise, groups of reports from different sources cannot be properly correlated, nor can the correct value always be placed on any particular group of reports. Some aspects of the performance of the Wassermann reaction show no essential variations with different systems; in the case of other points, there are variations, and it has been considered worth while to give the following brief description of the technic employed by us in the present series.

Technic;[14] *Hemolytic System.*—Corpuscles: We used washed sheep's corpuscles, 5 per cent. suspension in 0.085 per cent. sodium chlorid solution, 0.5 c.c. being taken.

Amboceptor: The serum of rabbits immunized against the washed sheep's corpuscles was used, 2 titer units being taken.

Complement: Fresh serums of guinea-pigs, undiluted, was used, 0.05 c.c. being taken.

The titers of various amboceptors varied from 0.0003 to 0.00004. Very satisfactory amboceptors from the points of view of both titer and stability were obtained by the method recommended by Coca.[15] The amboceptor was always titrated before performing the tests.

Antigens: The type of antigen used in all the tests was the acetone-insoluble variety, consisting of a saline suspension of a methyl alcohol and ether solution of the acetone-insoluble fraction of an ethereal extract of the residue after evaporation of an alcoholic extract of minced beef heart. This type of antigen was used in twice the amount, giving complete inhibition of hemolysis with syphilitic serums, this amount being one-tenth, or less, of the amount giving anticomplementary action by itself. With alcoholic extracts of guinea-pig hearts, used in some of the cases, as satisfactory results were usually, though not always, obtained.

14. The technic is similar to that in use at the laboratory of the Boston City Hospital.

15. Coca: Jour. Infect. Dis., 1915, xvii, 2.

Cholesterin antigen, 0.4 per cent. cholesterin (Kahlbaum) in absolute alcohol, was used in over 200 of the tests, but the results with this antigen are of more value in following antisyphilitic treatment than in aiding the diagnosis. Of 220 cases in which the tests were made with this antigen and with the acetone-insoluble variety, there were 202 in which there was close accord in the results; of the remaining eighteen tests, thirteen showed partial fixation with the cholesterin, and none with the other antigen, and five gave almost complete hemolysis with the latter and complete with cholesterin.

Our experience with cholesterinized antigens tends to confirm the conclusions drawn by other workers with these antigens, that cholesterin added to alcoholic extracts makes them more sensitive as antigens in the Wassermann reaction, but less specific. Recent work by McClure and Lott[15] makes for confirmation of this opinion.

For use in the tests the patient's serum was inactivated at 55 C. in a water bath for thirty minutes. The method of performing the tests was to place 0.1 c.c. of the inactivated serum from each patient in separate tubes (100 by 12 mm.). To each tube there was then added complement, amboceptor, and antigen, in the amounts above indicated, the bulk of liquid in the tube then being made up with saline solution to 1.1 c.c. The tubes were then incubated at 37.5 C. in a water bath for thirty-five minutes, when the corpuscle suspension was added to each tube and the tubes returned to the water bath for one hour. Controls with known negative and positive serums were run simultaneously. Tests showing any degree of inhibition of hemolysis were repeated without antigen to check anticomplementary action of these serums.

Results and Interpretation.—Positive reactions have been grouped in three classes. Those in which there was complete inhibition of hemolysis have been designated as $+++$; those showing a considerable degree of inhibition, but distinct hemolysis above the unhemolyzed corpuscles, as $++$; and, lastly, those with hemolysis almost complete, but with undissolved corpuscles in small amount still remaining, as $+$. A $+$ result alone has almost no value in diagnosis; it sometimes is of help when occurring in the course of treatment after a $+++$ result. The $++$ result with distinctly suspicious clinical signs may clinch the diagnosis of syphilis. The $+++$ reaction gives a positive diagnosis, but in the absence of any suspicion clinically, a repetition of the $+++$ reaction should be obtained. When the clinical picture is entirely negative and the Wassermann test is $+$ or $++$, a repetition on the blood collected later will frequently be negative; conditions other than syphilis, which may sometimes give partial inhibition of hemolysis in the test, are a few acute

16. McClure and Lott: Am. Jour. Med. Sc., 1916, cii, 5.

infections, during the period of elevated temperature especially, and certain chronic affections, such as tuberculosis. These transitory nonsyphilitic + and ++ reactions are infrequent. It may be of interest to note that of fourteen cases of eczema in the present series, without any suggestion of syphilis, four gave a + or ++ Wassermann. Conditions giving false positives or false negatives in the adult are not considered here.

(B) LUETIN TEST

We have applied the luetin test in 170 cases, nine syphilitic, 161 nonsyphilitic. Among the syphilitic cases there was one positive (pustular) reaction, one suspicious (papular), and seven negative results. Among the nonsyphilitics there were four positive reactions (one pustular and three papular), eight suspicious, and 149 negative. Thus, this particular test was of little diagnostic value in our series. The material used was direct from Noguchi's laboratory, and his written directions were carefully followed. Our cases are too few in number, however, to warrant any conclusions as to the diagnostic significance of the test.

ANALYSIS OF CASES

Our whole series of 695 cases, studied according to these methods, has been divided into the syphilitic and the nonsyphilitic classes, brief and condensed analyses of which are here given.

Cases Considered Syphilis.—We have accepted twenty-three cases as undoubtedly syphilitic. They may be grouped as follows:

Group 1, cases with distinct clinical signs, but negative Wassermann reaction, one case.

Group 2, cases without clinical signs, except poor nutrition and general adenopathy, but with Wassermann reaction +++, six cases.[17]

Group 3, cases with both clinical signs and positive Wassermann reaction +++ in fifteen cases, ++ in one case, sixteen cases.[18]

Thus, six of the twenty-three cases had no clinical manifestations of the disease, and a diagnosis is impossible except by the presence of a complete or +++ serum reaction.

Seven of the twenty-three patients died. Necropsies obtained on three of these showed syphilitic changes in all of them.

Cases Not Considered Syphilis.—The cases considered as nonsyphilitic number 672, and group themselves in more or less definite classes. In the first class there is nothing suggestive clinically and the Wassermann reaction is negative. They number 640. In most of these cases

17. Diagnosis was confirmed by necropsy in one case.

18. Two diagnoses were confirmed by necropsy. Spirochetes were found in the liver.

the test was done on the blood once only, in six on the blood twice, in sixteen on both the blood and spinal fluid, in one on the spinal fluid alone.

Doubtful Cases.—Three children with a single negative Wassermann and two with two negatives, all clinically suspicious, have been grouped in this class:

Maurice R. had a family history which was suggestive, but otherwise negative. One Wassermann test was made, which was negative.

Mike M. showed epitrochlear nodes and an enlarged spleen as the only signs. One Wassermann was made, which was negative.

Caroline R. had three miscarriages. A luetin test was positive, which was only suggestive, and one Wassermann test was made, which proved negative.

Mildred H. showed keratitis and adenopathy. Two Wassermann tests were negative and one luetin test was positive.

William K. showed suspicious teeth and general adenopathy, including enlarged epitrochlears. Two Wassermann tests were made, both of which were negative.

For statistical purposes, these children cannot be regarded as syphilitic, yet for their own future development, they should be watched, and repeated serum tests should be done.

Another class comprises seventeen cases with no clinical signs, but with an initial + or + + Wassermann and a subsequent negative reaction. Included in this class, however, are two exceptions, slightly suspicious clinically: Verna H., nose slightly flat, Wassermann + +, later negative; Victoria O., six weeks old, eruption on face and buttocks for two days, Wassermann +, later negative.

There is still another group of fourteen cases in which only one test of the blood was made, giving either a + or + + reaction. None of these patients had the slightest suspicion of syphilis clinically. Consequently, in view of our interpretation of an incomplete reaction, we cannot accept them as cases of syphilis.

One more nonsyphilitic case needs special mention. It showed no clinical evidence of syphilis; the Wassermann on the blood was negative, but + + on the spinal fluid. The case was one of tuberculous meningitis.

Serum tests have been done on the mothers of sixteen nonsyphilitic children, which proved to be + in one, negative in fifteen.

CONCLUSIONS

Statistics as to frequency of any given disease must be based on large numbers of patients, carefully and accurately studied as to diagnosis.

The diagnosis must be made after judicious weighing of all the evidence, both clinical and laboratory.

Study of the literature on the incidence of hereditary syphilis shows a wide range of results, it being variously estimated at from 2 to 14 per cent., in Europe and America.

Intensive study of a group of 695 patients in The Children's Memorial Hospital, during the winter of 1915-1916, the study embracing both clinical and laboratory methods of investigation, shows an incidence of 3.3 per cent. of hereditary syphilis.

The amount of hereditary syphilis among the hospital infants and children in four large cities of the United States, New York, St. Louis, San Francisco and Chicago, appears to range from 2 to 6 per cent.

We are indebted to Dr. Noguchi for the luetin used. Our thanks are also due to Dr. A. B. Schwarz, Resident Physician, for much valuable help in the prosecution of this work.

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CLINICAL COURSE AND PHYSICAL SIGNS IN HEREDITARY SYPHILIS OF EARLY AGE*

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Even a casual reading of modern textbooks shows a marked and irreconcilable variation in the descriptions of infantile syphilis. It seems wiser, therefore, to write only of such portions of the subject as have come within personal experience, rather than to attempt a finished treatise, which must, of necessity, include quotations or adaptations from others. This paper will therefore contain few quotations and few conjectures or theories, and will show very serious omissions, if one expects an exhaustive treatment of the subject.

The terms applied to syphilis of the infant need definition: "Infantile syphilis" includes hereditary, congenital and early-acquired syphilis. "Hereditary syphilis," strictly used, refers only to those cases in which the parents, one or both, were syphilitic at the time of conception. "Congenital syphilis" refers to those cases in which the mother is infected during pregnancy.

The last two terms are often used interchangeably, and the distinction between the children included under the different terms is little known, but there should be a distinction made between a fetus syphilitic ab initio and one rendered syphilitic after a healthy start. Studies in this direction have not been sufficient to allow accurate distinction, but it will probably develop that the congenital defects, the dystrophies, so common in syphilitic babies, are practically confined to hereditary cases. The term "hereditary syphilis" is often contracted to "heredosyphilis."

The relation between parents and offspring has been, and still is, the subject of grave discussion. Clinical observation allows a few statements, without any attempt at theory, which, it seems, might be universally accepted. Syphilitic children are born when the father is syphilitic, when the mother is syphilitic, and of course, when both parents are syphilitic. A pregnant woman who becomes syphilitic transmits the disease to her fetus. A baby born syphilitic may suckle its apparently healthy mother with impunity. A syphilitic mother may suckle her apparently healthy baby, born while she was syphilitic, with impunity.

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There may be exceptions to these rules, but not sufficient in number to invalidate their general truth.

Hereditary syphilis occurs in a great variety of clinical forms, differing according to the disease of the parents and carrying out the original protean character of the disease. The disease may affect the whole organism, or be manifest only in a single organ. The variety is therefore infinite. The baby may show the severest form or present such an appearance of health that one is with difficulty convinced that it is in any respect syphilitic. The clinical course of these various forms is somewhat different. One class of children who show severe disease at birth, and might well be described as having early malignant syphilis, merits a special and separate description.

These children are usually premature. They are emaciated; they snuffle and cry hoarsely. An eruption is soon apparent of bullae, situated chiefly on palms, soles, wrists and ankles. These bullae are flaccid and partially filled with seropurulent fluid. Some of these burst and leave red, angry-looking spots deprived of their epidermis. The lips are cracked and ulcerated; crusts form at the nostrils. The liver and spleen are enlarged and digestion is evidently very imperfect.

These children nurse with difficulty because of the condition of the nose. They cry all night, as if in pain, and in the daytime when handled. They become extremely emaciated and usually die within a few days or weeks of their birth.

These extreme cases form only a small portion of the total number of cases of heredosyphilis, but they are striking. They are easily recognized; they have often been described and figured and form the ideal syphilitic baby for both lay and professional opinion. Their extreme emaciation has led to the use of the term marasmus as practically synonymous with syphilis. The extreme or malignant cases of acquired syphilis have been used in the same way as examples of the disease.

From these emaciated and feeble specimens all gradations appear, up to babies whose condition cannot clinically be distinguished from health. But soon these apparently healthy children, for the most part, show something which justifies at least a suspicion of a syphilitic heredity. The study of the younger children of a syphilitic family, those in whom the disease is poorly marked and late in showing itself, is the best possible preparation for the recognition of syphilis in doubtful cases. Evidence of intra-uterine disease is often revealed by careful study of the babies brought living into the world.

WAKEFULNESS

One of the early symptoms which ought to attract attention is obstinate wakefulness. The child cries almost unceasingly at night and cannot be pacified. During the day he is quiet, so long as he is unmolested, and sleeps; but every night there is the same unceasing cry.

In many of these cases the baby's cries are only increased by handling, and the cry indicates pain.

Many of these cases of wakefulness are due to disease of the bones and their characteristic nocturnal pains similar to those affecting adults with acquired syphilis. The matter will be further discussed under the head of bone syphilis.

SNUFFLES

Nasal catarrh attacks a very large proportion of syphilitic infants, and gives rise to a most characteristic symptom. It appears early, often, if not always, preceding the eruption. It shows itself at the beginning by difficult and noisy respiration. The mucous membrane of the nose becomes swollen, and partially closes the nasal passages. A nasal discharge appears and increases, still further occluding the passage, and acts as a valve with each respiration, which becomes noisy. The symptom thus caused is known as snuffles. The discharge from the nostril is seropurulent in character at first and often streaked with blood. In severe cases this discharge runs down over the upper lip, which becomes reddened and excoriated. The difficulty of respiration increases; the discharge becomes purulent and dries into crusts, which may entirely close the nostrils and oblige the child to breathe through the mouth. In such cases nursing becomes difficult and often impossible; the child, obliged to relinquish the breast every moment to get breath, is fed very imperfectly, and sometimes weans himself.

The nasal symptoms may be very persistent, being the first to appear, and continuing months after other symptoms have vanished. In some cases the snuffling is not very noticeable so long as the child lies quiet and breathes through the mouth, but the difficulty becomes at once apparent if he is disturbed, and even more marked when he takes the breast.

Marshall quotes from Gastou a discussion of rhinitis in several forms which is quite striking and well worthy of quotation:

> Gastou describes the following forms: (1) Anterior rhinitis, which only differs from simple coryza by its long duration and the occurrence of fissures and erosions about the nose. This form is generally benign. (2) Posterior rhinitis, which is accompanied by slight discharge, but causes troubles of respiration and deglutition. This form is readily curable by mercury. (3) Subacute adenoiditis, which is rarer than the above, and generally follows them. It begins with acute pharyngitis, and continues with symptoms of adenoid vegetations. It is often complicated by otitis, laryngitis, and bronchopneumonia. It is cured with difficulty, and always leaves an inflammatory residue, which later on develops into adenoids. (4) Suffocating rhinolaryngitis, which is sometimes fatal soon after birth. The mucous membrane is dry and swollen, and its sensitiveness causes spasm of the glottis and sudden death. (5) Septic rhinopharyngitis, which is usually a complication of the other forms. This may be the origin of infectious lesions affecting other organs. In the acute form there is a fetid seropurulent discharge; in the subacute form, laryngeal and pulmonary complications, which are often fatal; in the chronic form, signs of septicemia, with visceral lesions and cutaneous ulcerations.

ADENOIDS

Few children with the snuffles of hereditary syphilis escape a diagnosis of adenoids and an operation. The symptoms are the same, whether the breathing is obstructed by adenoids or by narrowed nasal passages, such as occur in heredosyphilis. In syphilis relief is seldom obtained by operation, and we find the operation repeated and sometimes a third operation being done.

The upper jaw is known to lack proper development, so that the upper incisors fail to meet the lower, as was pointed out by Dr. Hutchinson in his observations on the deformity of the upper central incisors known by his name. The very high arched palate is another example of a deformity in the same bones; and Roentgen-ray studies of the facial bones show that the nasal passages are decidedly narrowed, so that the symptoms attributed to adenoids are really due to congenitally narrow nasal passages occluded by the swollen mucous membrane.

The objection to operations on syphilitic snuffles for adenoids is not alone that it is generally useless, but also that it exposes the physician to risk of inoculation. I have had the unpleasant duty of treating one enthusiastic operator for chancre of the finger. I have been told of another case, and even two cases are enough to warrant hesitation in doing an ill-advised and gratuitous operation.

CRY

Syphilitic babies, especially those in whom the snuffles is marked, have also a peculiar cry. It is at once hoarse and high pitched. It may not be diagnostic, but its character is such as to indicate that the same condition which causes the snuffles involves also the region of the vocal chords. Like the disease of the nose, the pathologic condition varies from simple inflammation and swelling of the mucosa to actual ulceration of mucous membrane and destruction of soft parts and cartilage.

MARASMUS

The marasmus of syphilis sometimes appears in infants who show in themselves little other evidence of the disease, and continues until the baby is reduced to the condition of a living skeleton. In breast-fed or carefully nourished infants who continue to waste without evidence of other disease to explain the phenomenon, a suspicion of syphilis should always be aroused, and a diagnosis may sometimes be made from the family history.

The term marasmus has become a synonym for hereditary syphilis in death certificates, for few deaths from hereditary syphilis are reported as such. Marasmus has very properly been dropped from most nosologies, but instead of forcing the certifying doctor to make a proper return, so far, it seems to result in still wider falsification of death returns.

LOSS OF WEIGHT

The healthy infant loses weight for a few days, but soon regains the loss and continues to gain. The syphilitic infant gains much more slowly, even in spite of the utmost care in feeding.

There is, in the Syphilitic Department of the Massachusetts General Hospital, under the care of Dr. Morton Smith, a baby, K., admitted on February 28 at the age of 3 months. Its mother has a positive Wassermann; the whereabouts of its father is unknown.

The baby was premature, was breast fed for one week, then had two breast feedings per day. On its seventh day it was admitted to the eye and ear infirmary with ophthalmia (character not reported), and remained there for six weeks. It had an eruption on the buttocks at 6 weeks, which became universal. Since discharge from the Eye and Ear Infirmary it has failed to gain weight. It is poorly developed, almost marasmic. It has fissures about the anus, definite temporal baldness, and hair thin generally. It has general glandular enlargement, occipital, submental and inguinal. Its nasal bones are rudimentary and it has slight snuffles. The liver is 2.5 cm. below the costal margin, and the spleen is just palpable. A soft systolic murmur is perceptible at the apex. It had marked fat intolerance during its stay in the hospital. Paracentesis of both ear drums has been necessary.

It has been most carefully tended and its feeding superintended by doctors from the children's department; but in spite of every care it has gained with wonderful slowness.

ADENOPATHY

Syphilis shows a marked tendency to involve the lymphatic system. The systematic examination of lymphatic nodes is part of the routine examination for suspected syphilis in the adult. The glandular system is of equal importance in the hereditary cases, though the opposite has usually been taught. The lymphatic nodes have the same characteristics as in the acquired disease; that is, they are multiple, noninflammatory, not painful, perfectly distinct and movable. Only occasionally do they suppurate except in the neck, where they are regarded by many clinicians as evidence of tuberculosis. The peribronchial glands and those of the omentum and mesentery have been found enlarged in postmortem examinations. The peribronchial glands occasionally play an important part in the clinical history of the affected child.

SKIN

On those cachectic subjects in whom emaciation is marked the skin hangs in folds, but such wasting is little noticeable in the less seriously affected babies. In many subjects the skin has a pale, sallow, earthy, sometimes yellowish hue which is regarded by some writers as

characteristic. Wegner, in his article on osteochondritis, suggested that the anemia and pallor might be due to disease of the bone marrow. In a few cases under observation, extreme pallor and marked bony changes have coincided. The change in the spleen must also be suspected.

The skin lesions of hereditary syphilis are marked by a tendency to become confluent and form large plaques, and also to desquamation and ulceration. Perhaps the multiform character of syphilitic dermatoses is more marked in infantile hereditary disease than in the adult acquired.

The most common eruption of heredosyphilis is the maculopapular, sometimes one element predominating, sometimes the other. Often the first evidence on the skin is the redness of the soles. This redness usually shows first on the heels, where it is darker colored than the rest of the sole and actually shines. Desquamation is common, often in flakes, which are very large in proportion to the size of the foot. Distinct papules are sometimes evident in the midst of the general redness. The palms show the same characteristics, though desquamation is even more common in the palms than in the soles.

The maculopapular eruption is usually first seen under the diaper in discrete lesions of perhaps half an inch in diameter. It may be confined to this region, but may extend over the whole body, varying very much in the total number of lesions. The color is the same dusky red, so difficult to describe in adult disease; the difficulty lying very largely in the fact that no one term can describe its varying appearances. Ulceration of separate papules is very common in the warm, moist region beneath the diaper.

Cracks and ulcerations about the lips, especially the corners of the mouth, are common. These ulcerations are transverse to the borders of the lips and radiate from the corners of the mouth. Such cracks and fissures occur with varying severity. Similar fissures radiate from the anus. The scars left by these fissures are of great value in diagnosis in later childhood and early adult life. They are referred to ulcerations of infancy. Some observations of late seem to justify the belief that these cicatrices are occasionally due to intrauterine disease. When I have made the remark that certain children must have had very sore mouths in infancy, the mothers have disputed my statement, and careful examination has occasionally shown cicatrices already existing, even in early infancy. A case in point shows a baby's face with abundant active ulcerations of the lips. About the mouth and on the cheeks are marks probably of ulcerations which were prenatal, possibly failures in development, similar to such defects as the failure of development of the nails, an example of which Dr. Wile published not very long ago.

Confluent Macula.—The macular eruptions often coalesce into large plaques on the face, about the genitals, and in the folds of the neck.

They may form such a plaque about the nose and mouth, extending on the forehead and chin, with an outline which hints at an original formation from circular spots which have united and with smaller distinct and separate circular spots in the neighborhood. The plaques are reddish or coppery in color, slightly raised. They desquamate rather freely. One unfamiliar with them might mistake them for eczematous patches, but they are quite distinctive and their distribution is diagnostic.

Such a plaque, covering the vertical middle third of the face, spreading over the eyebrows above and including the nostrils, closed by crusts, with lips cracked, ulcerated and bleeding, makes a characteristic picture.

Annular lesions occur with the same frequency as in acquired disease and in greater numbers on a single individual. One baby showed several circles on the neck, the wrists and one buttock and thigh were practically covered. They intersected and showed entire circles and segments of circles. They had been regarded as ringworms, according to the mother. One patient showed a series of rings arranged about the anus, which had ulcerated under the influence of heat and moisture. Another showed a series of intersecting rings on one buttock, so delicate that they could only be seen in certain lights.

Boils, Abscesses.—Occasionally a series of "boils" appear on a syphilitic baby. These are distributed widely over the body, six, eight or ten in number. They have a diameter of one-half or three-fourths inch. They open by a little hole in the center. In fact, they behave like gummas of the skin, which undoubtedly they are. Those cases in which they occur are usually severe. They may occur alone or as part of a general eruption.

More distinct abscesses occur occasionally and seem of a different nature.

Bullous eruptions occur at a very early age. They are either present at birth or appear very shortly after. The lesions occur about the hands and feet, though they are not necessarily confined to these localities. The bullae vary from one quarter to three quarters of an inch in diameter. They are flaccid, only partially filled with turbid fluid, which is sometimes mixed with blood. They are easily ruptured and the loosened epidermis partially covers the reddish base. They indicate a serious form of disease, which usually, but not always, ends fatally. Other forms of eruption may be present at the same time.

ONYCHIA

Onychia of the nails is quite common in syphilitic infants, but it varies in character. All the nails may be affected, or more commonly only a minority, perhaps only one. Usually there is thickening, dis-

coloration and gradual separation of the nail from its bed. It may be a noninflammatory process, attracting no attention and only seen if looked for. On the other hand, there may be inflammation and suppuration, with all the pain and tenderness that attends onychia in the adult, and paronychia. In both forms the nail may be shed repeatedly before a permanent nail is produced.

ALOPECIA

Loss of hair is one of the important characteristics of heredosyphilis. It is found at birth in a large proportion of cases, being one of the evidences of intrauterine disease. It occurs in various forms, but seldom, if ever, as a complete loss. It is usually a general thinning of the hair. Sometimes it shows chiefly as an exaggeration of the natural bays over the temples. The loss of eyebrows at the same time may be taken to mean syphilis. The remaining hair often presents a dry and unhealthy appearance.

CRANIAL EXOSTOSES

Cranial exostoses of syphilitic infants were described by Parrot, who regarded them as incontestible proof of syphilis. They are flattened elevations of variable prominence and extent, of a circular contour, sometimes elongated in one or two directions. They have four seats of predilection, the two frontals and the two parietals. Ordinarily they are symmetrically placed in regard to the frontal and sagittal sutures, but not always. These cranial exostoses are by some attributed to rachitis, but they occur long before the age at which rickets occurs and in conjunction with very evident syphilis.

Disease of the bones is one of the most important of syphilitic manifestations. It begins before birth and during infancy furnishes evidence of intrauterine disease; it is a cause of some of the most distressing of infantile maladies, and plays a very important part in differential diagnosis. It needs careful study because of the danger of mistaking it for rickets, scurvy, tuberculosis or some of the rarer forms of bone disease. Hereditary bone syphilis may present all the forms of the acquired disease occurring in bones that have reached their growth. In addition to these it has certain forms of its own, as it occurs in bones in their formative period.

Perhaps the most important of the manifestations of syphilis in the infant skeleton is the retarded ossification at the line of growth known as osteochrondritis. This pathological change was described by Wegner, assistant in Virchow's clinic in 1870, though other observers have contributed to our still imperfect knowledge. This change is confined to the long bones. It is not found in all syphilitic infants, or in all the bones of any one baby. There is also present at the same time perios-

titis, sometimes involving seriously a number of bones. These changes require serious anatomical research. They have been studied by frozen sections, but radiologic pictures disclose the condition of the whole skeleton at one time and during life.

As shown in the Roentgen-ray picture, the line of demarkation between diaphysis and epiphysis is broader and in the extreme development of the disease there is shown a displacement of the epiphysis. There is almost always marked periostitis of some bones. When one looks on the radiologic picture, it is very easy to understand why the baby cries when he is moved and why he cries so unceasingly. The subluxation of the epiphysis may be recognized in the radiograph. It is the cause of the pseudoparalysis known as Parrot's.

BABIES BORN AFTER THE ADMINISTRATION OF SALVARSAN TO THE MOTHER

It is pretty evident that salvarsan administered during pregnancy to mothers who have previously borne syphilitic children brings about a great improvement in the succeeding baby, but does not always entirely remove the syphilitic taint. These babies are plump and apparently healthy, but with square heads and scanty hair or other suspicious condition. One of them had a very marked alopecia; one had a few flat papules about the face, which were considered to be syphilitic. This child had several abscesses, one of which communicated with the elbow, which healed with a stiff joint.

Of course the condition of the family in regard to syphilis will have much to do with the result. In one case of such a baby as is described above, the pregnant woman received an inoculation of syphilis in the tonsil quite early in her pregnancy. The syphilis was allowed to gain considerable headway before it was recognized. She had had an extremely well-marked secondary eruption for some weeks before she received any treatment. She then received salvarsan and mercury. The child was the child of parents healthy at the time of conception and it is impossible to know just how much credit should be given the salvarsan.

Babies of parents treated by mercurials resemble those whose parents were treated by salvarsan. Whether it is possible to draw a distinction between the two classes of babies remains undecided, but the babies seen after the administration of salvarsan are especially noticeable.

TWINS

It often has been asserted that one twin may be severely affected while the other escapes entirely. There are at present two pairs of twins in attendance at the Massachusetts General Hospital outpatient department. Of the first pair, one has well-marked snuffles, marked

pallor, shining soles and maculopapular syphilis, confined to the region of the diaper and inclined to ulcerate, and marked glands in the groin. It is practically unable to move the left arm, though it moves its fingers. It cries when either of its arms or legs is moved, but has not entirely lost the power of movement. All the bones of the extremities seem to be tender to touch. The second baby, a girl, when seen had a much better appearance, was fatter and had better color, but had a confluent macular eruption specially marked on the right buttock.

In the second pair of twins the children are about equally affected, and are both markedly syphilitic.

Van der Bogert[1] reports twins, one mongolian, with positive Wassermann, the other normal, with negative Wassermann.

DIAGNOSIS

The diagnosis of hereditary syphilis in the infant may be the simplest possible in the severe cases in which the wasting and external manifestations are prominent, or it may present one of the most difficult problems in medicine.

The syphilographer is occasionally asked for an opinion in regard to a very young baby which presents no certain signs. It is often necessary to formulate his opinion on a series of symptoms, no one of which is sufficiently marked, by itself alone, to permit a certain diagnosis. He should listen for noisy breathing, not evident when the baby is sleeping, and listen to its cry. The hair should be carefully observed and the veins of the scalp. The soles need special inspection. The characteristic redness appears first on the heels. It is often marked on the heels when it is not noticeable on the palms. Occasionally, it is the first and only sign present for a time. Careful radiologic study is going to be a great aid in diagnosis.

Fournier[2] says:

> Given a patient upon whom we suspect a hereditary syphilis, never fail to examine the skeleton, bone by bone, without allowing ourselves to be deterred from that examination by the absence of a history of an anterior bony lesion, or even by the denial of such lesions. Since it is possible that from such an examination will come the demonstration of an unknown bony lesion, ignored or even forgotten, and it is unnecessary to say how great will be the interest of such a discovery.

The advantage of such an examination has been greatly increased since the advent of the Roentgen ray, which confirms the testimony of our fingers and reveals a still greater number of lesions which escape the most careful manual investigation, and although that advice was given in regard to children of more advanced years, it has its application to infancy.

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1. Van der Bogert: Am. Jour. Dis. Child., 1916, xi, 55.
2. Fournier: La syphilis héréditaire tardive, 1886, p. 274.

CLINICAL SIGNS AND DIAGNOSIS OF LATE HEREDITARY SYPHILIS *

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RELATION OF LATE TO EARLY SYPHILIS

The division between early and late hereditary syphilis is largely arbitrary, but, in general, the term "late" is applied to those manifestations which are analogous to the tertiary and quarternary symptoms of acquired syphilis. Having the division on such a basis causes the two types to overlap considerably in regard to age. We may have late lesions as early as birth and early lesions as late as 5 or 6 years of age. As to the upper age limit at which manifestations may occur, none has been established. Changes peculiar to hereditary syphilis are found regularly in the third decade and there are some, notably Fournier, who claim to find manifestations with considerable frequency up to the seventh decade.

The clinical cause of the development of the late type of lesion, as well as the longer or shorter interval between the manifestations of invasion and the late lesions, has remained largely unexplained. The most reasonable explanation is that offered by the hypothesis of Henry Head,[1] according to which there develops a sensitization on the part of whatever body cells come in contact with the spirochete during the invasion or early period. The fuse of the tertiary lesion is then touched off by the appearance in the neighborhood of these sensitized cells of a few spirochetes, which make their appearance from whatever viscus or part in which they have been quietly reposing. Such a course of events seems highly probable and is the only explanation up to the present time which harmonizes with the facts. The division into early and late, in the light of this hypothesis, is relegated to its proper place. It is not a matter of when these organisms start on their journey, but where they go.

During the latent stage, previous to the onset of the late lesion, there may be no stigmata whatever, the child may be above the average in mental and physical development and the only evidence of a persist-

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* From the Department of Pediatrics, Washington University Medical School, St. Louis.

1. McIntosh, Fildes, Head and Fearnsides: Brain, 1913, xxxvi, 1. Fildes and McIntosh: Brain, 1913, xxxvi, 193. Head and Fearnsides: Brain, 1914, xxxvii, 1. McIntosh and Fildes: Brain, 1914, xxxvii, 141.

ing infection may be a positive Wassermann reaction. There is but little literature on these latent cases, which at any time quite unexpectedly develop an active lesion. The question has arisen whether or not in such cases the patient should be treated. Since the Wassermann reaction is an expression of activity on the part of the spirochetes, it has seemed advisable to carry out the treatment just as if an active manifestation were present. The interesting occurrence in our patients so treated has been the frequent onset of an interstitial keratitis shortly after beginning an intensive treatment, comparable to the aggravation under intensive treatment of an interstitial keratitis that had already begun. This latter has occurred in a large number of our cases. In spite of this unpleasant complication, we still believe that in a latent case a patient should be treated. The very fact that this complication occurs is proof of a potential lesion not yet manifest and it is probable that it would become manifest later without treatment.

NERVOUS SYSTEM MANIFESTATIONS

The contributions of Head[1] and his co-workers are probably the most important on the subject of syphilis in the recent literature, and though dealing exclusively with nervous manifestations of acquired syphilis, the ideas are equally applicable to the hereditary infection. The acceptance of their views will increase our ability to classify and study syphilis of the nervous system and avoid much confusion that now exists. They divide syphilis into two main types, syphilis meningovascularis and syphilis centralis, both of which are usually preceded by early symptoms, which they enumerate as follows: Changes in character, behavior, aptitude and memory; disturbances of balance between emotion and reason, headache, changes in sensibility, all forms of disturbance of sleep, nocturnal psychoses, neurasthenic symptoms, attacks of shivering and fever and neuralgic pains due to root lesions. Syphilis meningovascularis includes all the subacute, chronic, tertiary and gummatous lesions, all having the same essential pathology, whether secondary or tertiary. Syphilis centralis includes all the so-called parasyphilitic affections. These have been considered by the majority of writers as purely degenerative processes, primarily, and vascular and glial proliferations, secondarily. Head holds that this lesion has essentially the same pathology as all other nervous lesions and is a reaction, not a degeneration. He holds that both the tertiary form and parasyphilis are due to hyperallergie, as already mentioned. The difference in the anatomic consequences depends on the nature of the tissues involved, which is blood vessels and their connective tissue in one case and highly specialized structures in the other. In the central variety the resulting clinical manifestations depend on the route and the destination of the invading spirochetes, which is along the

posterior columns and roots in the case of tabes and in certain cerebral convolutions in the case of paresis. All varieties of borderline cases between tabes and paresis as well as manifestations which fit into neither group are to be expected. The meningovascular variety is amenable to treatment, but the lack of benefit observed in the central type is due to the fact that nerve cells are already dead and even more to the fact that our present remedies can not reach the spirochetes. Often there is no active lesion to treat, for "instead of a flame we have dead ashes." The Wassermann reaction as standardized and determined by them and its behavior under treatment is used to a large extent in the differentiation between the central and meningovascular types.

Contrary to what is apparently the general impression, lesions of the nervous system in hereditary syphilis are quite common, occurring in nearly 50 per cent. of our late cases. Of the clinical diagnoses, cerebrospinal syphilis comprises much the largest group. This is due to the fact that syphilis of the nervous system assumes such infinite varieties that it is useless to attempt to separate manifestations into types. For clinical purposes cases may be grouped roughly according to the situation chiefly affected. The common pathologic lesion is a meningoencephalitis or myelitis, either associated with or caused by an endarteritis. Certain syndromes, because of their interesting features or of their frequency, will be briefly discussed.

Chorea.—Several authors[2] have recently interpreted their observations as showing the absence of relation between choreic symptoms and syphilis. We have observed a number of patients in whom both diseases existed and in but one was there any relation between the syphilis and the choreic symptoms. In that one case[3] the fact that the symptoms were due to syphilis seemed established by the therapeutic test. A maniacal chorea was converted into a mild case in twenty-four hours by a dose of neosalvarsan and was completely cured in the course of a few days by the same therapy.

Epilepsy.—Epileptiform seizures differing in no demonstrable way from idiopathic epilepsy may be the direct result of a syphilitic infection. Of our own cases of epilepsy about 20 per cent. were so caused. From the point of view of prognosis it would seem clearer to consider this manifestation in Head's scheme of classification since both types occur.

Multiple sclerosis probably does not occur in childhood, but not infrequently we find patients presenting symptoms quite similar to those of this disease. One such case, which was apparently due to

2. Comby: Arch. de méd. d. enfants, 1915, xviii, 517. Koplik: Arch. Pediat., 1915, xxxii, 561.

3. Veeder and Jeans: Am. Jour. Dis. Child., 1914, viii, 283.

syphilis and which responded fairly well to syphilitic treatment, has come under my observation. The pathology of multiple sclerosis is essentially different from that of a case presenting similar symptoms due to syphilis. The latter symptoms are caused by multiple foci of encephalomyelitis, while multiple sclerosis is a myelin sheath degeneration, noninflammatory in character, vessels not being involved, with no secondary degeneration and the axis cylinder remaining intact.

Hemiplegia, in our own material at least, is the most frequent variety of acquired paralysis due to syphilis. Of twelve cases of hemiplegia, six apparently had a syphilitic basis. Savy[4] reports seven necropsies and Pehu and Gardere[5] one on this type of case and the findings in all were practically the same, an encephalitis associated with a syphilitic arteritis. These authors emphasize the fact that the pathologic picture anatomically and histologically differed in no way from other forms of encephalitis and conclude that it is necessary to place syphilis among the infections capable of producing acute encephalitis and give it an important place in the etiology. Acquired paraplegia and diplegia may also occur as a result of syphilis. Paraplegia occurring as a manifestation of late syphilis is often of the spinal or flaccid type, though cerebral symptoms are usually associated. The onset may be sudden or gradual, with pain and sensory disturbances. Such symptoms may be caused by a circumscribed myelitis or gumma, or by a diffuse myelitis over a whole cross-section of the cord. An endarteritis is usually the cause of the myelitis or at least is associated with it.

Mental deficiency of varying grades is a very common finding as a result of syphilis. When occurring as a manifestation of late syphilis, it is more often found associated with other symptoms, such as fixed pupils, paralysis or a complicated brain syphilis. Taking all cases of mental deficiency, we find the number due to syphilis is relatively small, but among the late syphilitics more than one third in our material show this disorder.

Brain tumor symptoms caused by syphilis are relatively rare. When present, they are usually caused by either a gumma, encephalomalacia, or a circumscribed meningovascular process.

Parasyphilis, meaning syphilis centralis in the terminology of Head, is a rather frequent finding in children, but in its usual sense, meaning optic atrophy, tabes and paresis, it is uncommon. We have observed one case of primary optic atrophy in a patient as young as 4½ years. Tabes is seldom diagnosed in children, probably not because it is so rare, as it is indefinite as compared to adults. Ataxia, disturbances of gait and Romberg's sign are more unusual and the absence of patellar

4. Savy: Quoted by Pehu and Gardere (See Footnote 5).
5. Pehu and Gardere: Arch. de méd. enfants, 1915, xviii, 330.

and Achilles reflexes is not so constant as in adults. The Argyll Robertson pupil is considered a cardinal symptom. Optic atrophy is present in a large percentage of cases and is usually the earliest symptom. The first signs usually appear late in childhood, though cases have been reported as early as 5 and 6 years. In our St. Louis material we have observed but one case, a girl of 18 years, presenting sufficient evidence to make a positive diagnosis. Cases showing diminished reflexes and pupillary changes have not been unusual, and some of these cases might very well be early cases of tabes.

Paresis in children is somewhat more common than tabes, the time of onset being most frequently between the ages of 12 and 16 years Cases have been reported at 8 years and under, but it is doubtful if it can be diagnosed so early. The characteristic symptoms are both psychic and somatic. In a young child the intellect is not sufficiently developed to show the psychic changes. A positive diagnosis could scarcely be made entirely on the somatic changes, which are merely those of syphilis. The main symptoms, especially as differing from adult paresis, may be summarized as follows: There is arrest of physical and sexual development. The face becomes expressionless. There are automatic sucking, smacking and chewing movements and humming, which rarely appear in the adult. Pupil changes are present early, but they may be merely sluggish instead of fixed. A special peculiarity is the early and frequent occurrence of epileptiform seizures, which have been spoken of as paralytic attacks. The psychic symptoms frequently have a sudden onset. There is a progressive defect in intelligence and judgment, without fixed ideas or hallucinations. Ideas of grandeur, when present, assume an infantile character. The child becomes apathetic, undemonstrative and gradually forgets all that has been learned. Occasionally there are outbreaks of passion, but mania never occurs. There are increasing disturbances of speech, the vocabulary diminishes and speech finally ceases, except a few unintelligible words. Gradually the somatic symptoms become more pronounced and the child becomes bedridden and death results from pneumonia, a paralytic attack, or sepsis originating in decubitis. Remissions, though common in adults, are rare in children. The duration of the disease is usually from three to five years, or even longer. Tabetic symptoms occasionally occur in addition to the paresis. The pathology of juvenile paresis differs but little from that of the adult type, except possibly the greater frequency of cord lesions in the former.

BONES

The most frequent lesion is a chronic osteoperiostitis, gummatous in character, involving chiefly the long bones. It is occasionally seen as early as the second year, but occurs most frequently after the fifth

year. It may occur in any part of the skeleton, but the site of greatest frequency is the tibia. The process as it occurs there is briefly as follows: The shaft of the bone is affected chiefly or exclusively. There appears on the crest a tender, painful swelling, the pain being increased on motion. Roentgen ray shows periosteal thickening over a considerable area, with its greatest thickness at the site of the nodule, where the bone itself is hyperplastic. Necrosis may take place at this site with resulting sinus. In some cases differentiation from tuberculosis offers considerable difficulty. More often the process is arrested without necrosis and a permanent deformity of the bone results, an outward fusiform curving of the involved surface.

Gummas also occur, located centrally in the bone, frequently resulting in bone necrosis with sinus formation. The tibia again is the most common site. The small bones of the hands and feet are not infrequently involved.

There occurs also a diffuse hyperplastic process developing chiefly in the long bones, notably in the tibia. This is usually quite chronic, often continuing over a period of years. The bone may enlarge to twice its normal size, the thickening being due to new periosteal bone layers. The process is not necessarily painful, there occasionally being no pain whatever. When it occurs in the tibia, there is frequently an anterior and occasionally a lateral curving. The disease is usually symmetrical and the deformity permanent. Lengthening of the involved bones is occasionally seen. Syphilitic bone hyperplasia, especially if occurring diffusely at one end of a long bone, may be confused with sarcoma, as in one case in our material. The deformities are differentiated from rickets by the age of onset, the nodular rounded shin, and the increase in size of the bone shaft.

JOINTS

About 10 per cent. of the late hereditary syphilitics show joint affections. Any joint in the body may be involved, though the knee and, secondly, the ankle are affected with much the greater frequency. A striking feature of these affections is their frequent association with eye syphilis. Often these are present at the same time, or one precedes the other by a few weeks.

In going over the literature one is struck by the absence of definite pathologic knowledge, and perhaps for that reason the lack also of a clear-cut clinical classification. Types as described are largely indistinct and one type tends to change to another.

There is the type[6] described by Clutton of simple symmetrical synovial effusion, chronic in character and without pain. It is insidious

6. Post: Boston Med. and Surg. Jour., 1915, clxxiii, 941.

in its onset and development, the first complaint being a stiffness of the knees and a sense of weight on walking.

There occurs also an acutely developing synovitis, with severe pain and loss of function. This type is without bone involvement as shown by the Roentgen ray and is the variety most frequently found in our material. From its clinical aspect alone it is easily mistaken for a tuberculous arthritis.

A variety frequently seen occurs with swelling of the epiphysis of one or both of the neighboring bones, and gross changes in the joint surfaces. These changes are gummatous in character, involving both the cartilage and bone and are associated with a chronic effusion and a thickened capsule.

A variety not infrequently observed is one resembling the clinical picture of arthritis deformans. The joint involvement is frequently multiple, affecting the small as well as the larger joints. There is a chronic effusion and irregular thickening and lipping of the epiphysis of adjacent bones. There is but little pain and the limitation of motion is merely mechanical.

Tubby[7] describes a chondro-arthritis, characterized by a recurring synovitis, with chronic inflammation of the neighboring bone. The disease is incurable and he classifies it as parasyphilitic. Joint involvement is more often primary, but it may be the result of extension of pericapsular or bone gummas. In such a case there is often an extensive formation of villi in the joint.

SKIN

Skin manifestations in late hereditary syphilis are largely of two types, a large and small nodular syphilid. The large syphilid is a gumma the point of origin of which is usually in the subcutaneous tissues. On account of its greater frequency this is the most important skin manifestation. It develops most frequently on the face or upper part of the legs and thighs. These lesions are at first indurated, often having a gray color with red borders. They respond quickly to treatment, but if neglected, break down, leaving deep ulcers. The ulcer has a scooped-out appearance, with an indurated border. On healing it leaves a white scar. It is not always easy to differentiate gummatous from tuberculous ulcers.

The small nodular syphilids are pea-size or larger circumscribed infiltrations, later becoming covered with a crust, under which necrosis continues, the whole increasing in size, the center becoming depressed and sometimes becoming serpiginous. The lesion may undergo resolution at any stage, but does not respond so readily to treatment as does the gumma.

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7. Tubby: Brit. Jour. Child. Dis., 1908, v, 49.

MUCOUS MEMBRANES

The lesions of the mucous membranes are largely gummatous ulcerations. They occur in the soft palate and pharynx, and gummatous infiltrations are occasionally observed on the epiglottis and in the larynx and trachea. Perforations seen in the soft palate are practically always from this cause. These ulcerations are usually without pain, have sharply defined, indurated borders and on healing leave a smooth, white scar, with a decided tendency to contraction. Adhesion of the soft palate to the pharyngeal wall is sometimes observed.

When gummas occur in the nose or hard palate they may have their point of origin in either the mucous membrane, the bone or the periosteum. In any case the final result, if they are untreated, is the same, either perforation or extensive necrosis of the neighboring bone and soft parts and in the nose causing a protracted ozena. When occurring in the bone there is often considerable pain associated.

EYE

Affections of the eye in late hereditary syphilis are very common and in our materiai ranked second only to those of the nervous system. The lesion most frequently found is an interstitial keratitis. This affection, though in the great majority of cases being caused by syphilis, is not pathognomonic of that disease. The usual age of occurrence is from 6 to 12 years, though in our own series we have one case at 3 months and another at 20 years. This manifestation, with insufficient treatment, frequently recurs in a few months or years, and from the viewpoint of treatment is often one of the most intractable of the curable affections of syphilis, sometimes requiring several years for cure. Both eyes may be affected at once, or there may be an interval of several weeks or months before the second eye is affected. As Hutchinson pointed out, there is a frequent association between keratitis and Hutchinson's teeth, and in the few cases we have seen having Hutchinson's teeth, this deformity was largely in association with keratitis. The frequent relation to joint disease has been mentioned elsewhere.

A choreoretinitis not infrequently occurs, which is characteristic of syphilis. Gummatous iritis is occasionally observed. Other eye manifestations of syphilis are more properly considered with the nervous system, lesions of which may cause strabismus, nystagmus, optic neuritis, optic atrophy, choked disk, temporary ocular palsies and fixed and unequal pupils.

EARS

Deafness is not infrequently the result of syphilis, and its common association with keratitis has been observed by many, notably Hutchinson. It is usually bilateral and affects girls with somewhat greater fre-

quency than boys. It has been considered as of three types.[8] The more common type is of insidious onset, without vertigo or other symptoms, complete permanent deafness developing in the course of a few weeks. The lesion is a chronic osteitis, leading to bone proliferation, which gradually more or less completely occludes the cavities of the internal auditory meatus and the bony labyrinth.

In the second variety vertigo is a marked symptom, which is accounted for by increased tension due to exudation. Tinnitus and subjective noises may also be present. With acute onset there is immediate destruction of the labyrinthine nerve endings by pressure alone. If the disease assumes a subacute or chronic course there may be exacerbations with recurring vertigo.

In the third type there is a nerve deafness due to central involvement of the parasyphilitic or central type.

LYMPH GLANDS

Lymph gland involvement as a cause for complaint is uncommon. Such a lesion is usually a gumma, involving either a single gland or a group of glands. These are hard and painless and there is but little tendency to break down. In one such case now under observation the glands have broken down, leaving in the neck an extensive ulceration six inches long.

There is but little tendency to a general adenopathy in late hereditary syphilis, and when this is found it is of no great assistance in the diagnosis.

RESPIRATORY

Affections of the lungs, as manifestations of late syphilis, are rare, and when they occur there are no characteristic symptoms. Large gummas may occur in later childhood, but of more frequent occurrence are small gummatous nodules in infancy. A chronic pneumonia of syphilitic nature has been described, which is followed by bronchiectasis and emphysema. In syphilitic children there is a tendency for all inflammations of the lung and bronchi to become chronic. The number of syphilitic children in our material who have contracted a most intractable chronic bronchitis is striking. The tendency for these children to acquire tuberculosis is well known.

Late manifestations in the larynx, trachea and bronchi are rare. Occasionally gummas occur. We have observed but one case of gummatous ulceration in the larynx. In such a lesion hoarseness and aphonia may be observed. The disease is painless and is diagnosed only by inspection. Untreated, such lesions are prone to cause stenosis from cicatricial contraction. Obstruction from the gumma itself has been observed.

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8. Yearsley: Brit. Jour. Child. Dis., 1908, v, 195.

CARDIOVASCULAR

Gross changes in the heart as a result of late syphilis are quite rare. Aortitis, when it occurs, is usually of a syphilitic nature, and aneurysm of the aorta is occasionally observed as a result. Arteriosclerosis is uncommon in children and is usually the result of syphilis. Endarteritis is not often diagnosed clinically, but is a frequent lesion found associated with cerebrospinal syphilis. A syphilitic endarteritis not infrequently causes a symmetrical gangrene of the extremities, one such case having come under our observation.

VISCERA

Visceral involvement is uncommon and, as for its clinical diagnosis, is rare. Splenic enlargement is frequently found, but this is usually a simple hyperplasia, and not a specific change. The spleen may show interstitial changes, either diffuse or circumscribed, and rarely a gumma is found.

The liver is most frequently involved, the lesions being either a gumma or a hypertrophic cirrhosis. Gummas in both the liver and spleen have been described as occurring in earliest infancy.

Chronic interstitial nephritis is said to be due in some cases to syphilis. We have observed what was possibly one such case, though how one can make a positive diagnosis of syphilis as the cause is not entirely clear. Diabetes insipidus has in certain cases been associated with syphilis. Both the adrenal and the testis may show interstitial changes and gummas. There are no important lesions of the stomach or intestine.

MISCELLANEOUS

Paroxysmal hemoglobinuria has been repeatedly described in relation to hereditary syphilis, and it is the opinion of many that it is pathognomonic of this infection. The exact pathology is not yet clear. It is evidently a blood dyscrasia, in which there is an autohemolysis following exposure to cold. The exposure is usually followed closely by a chill and fever. The amount of blood destroyed is usually small and probably corresponds to the amount that is actually chilled during the exposure. The free hemoglobin is rapidly excreted in the urine, 90 per cent. being excreted in the first two hours in an experimental exposure.[9]

Raynaud's disease is not especially rare as occurring in connection with hereditary syphilis. Its etiology and pathology is still unknown, though it is the opinion of many that these symptoms may be caused by syphilis. One case[10] already reported in detail has been seen by us.

9. Dennie and Robertson: Arch. Int. Med., 1915, xvi, 205.
10. Lisser: Arch. Int. Med., 1915, xvi, 509.

DIAGNOSIS

In the diagnosis of syphilis the Wassermann reaction, in competent hands, is invaluable, being positive in practically 100 per cent. of the late cases in childhood.

The value of the family history needs no emphasis. The occasional fact that all knowledge of syphilis is denied by the parents and both give a negative Wassermann has no especial bearing on the diagnosis in the child. Among our cases the father gave a positive reaction in less than 50 per cent. of those tested, even though he was the starting point for the infection in the family. The mother's reaction is positive more frequently.[11]

The early history of the patient, though helpful, is usually insufficient to make a positive diagnosis. However, some of the early lesions leave their permanent mark. An older child may give a history or show evidence of former lesions of the late type. The various signs and stigmata that may be present will be briefly discussed.

Cutaneous Scars.—Rhagades, or radial scars, about the mouth, the result of syphilitic infiltration in infancy, are produced by nothing else. To be characteristic, however, they must be definitely linear and not limited to the angles of the mouth. The same appearance may be produced about the anus. Old scars of gummatous ulcers usually have a characteristic appearance, being white and smooth and when found on the face or distributed along the tibia are almost positive proof of syphilis.

Mucous membranes may show scars of ulcerations similar to those on the skin. Perforations are usually permanent and are almost invariably due to syphilis.

Disturbances of development are sometimes observed following severe infantile syphilis. These are in no way pathognomonic. The body is undersized, the constitution is delicate and shows but little resistance to disease. Puberty is frequently delayed. Anemia is usually present and the patient has a sallow appearance.

Skeletal Changes.—Teeth: From the standpoint of frequency Hutchinson's teeth is not a valuable sign, though when present constitutes good, but not absolute, evidence of an early infection. The presence of two, widely spaced, instead of four upper incisors is very suggestive, especially if these are pegged or otherwise misshapen. A characteristic deformity of the first molars has been described by Moon.[12] These teeth are "reduced in size and are dome-shaped, through the dwarfing of the central tubercle of each cusp."

11. Jeans: Am Jour. Dis. Child., 1916, xi, 11.
12. Lucas, R. C.: Brit. Jour. Child. Dis., 1908, v, 1.

Head: Cranial bone disease, other than rickets, is rarely due to anything else than syphilis and usually leaves some deformity. There is nothing pathognomonic about the shape or size of the head, though evidence of an arrested hydrocephalus is suggestive.

Nose: Some of the milder grades of pug or saddle nose often prove to be congenital deformities rather than the result of a syphilitic necrosis.

Scaphoid scapulae, though suggestive, have not proved more useful than other disturbances of development.

Tibiae: Thickening and irregularities of the tibiae, especially if these deformities are extreme, make good positive evidence of infection.

Special Organs.—Eyes: Corneal opacities, though in no way a proof of syphilis, are often helpful in connection with the history. Fixed pupils, especially Argyll Robertson pupils, are very characteristic and with but few rare exceptions are pathognomonic. Irregular pupils and synechiae of the iris constitute good presumptive evidence. On ophthalmoscopic examination evidence of a former choroidoretinitis is found in persisting choroidal spots.

Ears: Deafness without obvious destruction in the ear, complete in the course of a few weeks, is almost pathognomonic of syphilis, though from the view point of frequency this occurrence is not very helpful. Syphilitic deafness was present in but 1 per cent. of our late cases, and among several hundred cases of late syphilis Hutchinson's triad occurred not once.

Voice: Swift[13] has recently directed our attention to a voice sign which has about the same significance as Hutchinson's teeth and scaphoid scapulae. This sign manifests itself in a harsh, rasping, monotonous, low pitched voice that is not amenable to any sort of treatment.

Nervous System.—There are few nervous manifestations pathognomonic of syphilis, but with a progressive acquired mental deterioration or paralysis syphilis is strongly suggested. The occasional occurrence of a positive Wassermann in the spinal fluid when the blood Wassermann is negative must be borne in mind. The Lange colloidal gold reaction is very helpful as a corroborative test, but in its present status syphilis could scarcely be positively diagnosed on that test alone. Other corroborative evidence of value is the presence of globulin and pleocytosis in the spinal fluid.

Rheumatism.—In the presence of vague and persistent affections which are commonly classed as rheumatic, we not infrequently find a rheumatic history lacking and a syphilitic history present. Attention has recently been called to this rheumatic group by several authors.[14]

13. Swift: Boston Med. and Surg. Jour., 1915, clxxiii, 619.
14. Stoll: Boston Med. and Surg. Jour., 1915, clxxiii, 606; see also Footnote 3.

The rheumatic pains may be periosteal, bone, muscular or nerve root pains, and are important from the view point of diagnosis, because they yield so readily to proper treatment.

Differentiating Syphilis from Tuberculosis.—This is a point of considerable importance in the welfare of our patients, and one which is not sufficiently appreciated. The difficulty in certain cases of differentiating syphilitic from tuberculous processes is encountered in any part of the body where both diseases tend to manifest themselves, especially in the bones, joints and lymph glands. After the application of all our diagnostic knowledge the nature of the process may still be in doubt or be incorrectly diagnosed. It has been the experience in our clinic[15] that the gross and microscopic pictures of the two diseases may be absolutely indistinguishable. In our opinion, and to a certain extent to our knowledge, many syphilitic processes are treated as tuberculosis, the diagnosis of tuberculosis being supported in some cases by a reliable pathologic laboratory. In such a case a positive Wassermann reaction and the therapeutic test may be our only means of diagnosis.

15. O'Reilly: Am. Jour. Orthop. Surg., 1914, xi, 431.

A COMPARATIVE STUDY OF THE LUETIN AND WASSERMANN REACTIONS IN INFANCY AND CHILDHOOD*

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In studying the symptoms of congenital syphilis, it is noted that many of the classical symptoms exist in cases which are not syphilitic, and the reverse is also true that cases of syphilis are seen with but few of the classical symptoms. For some time in observing these symptoms one of us (DeBuys) has been impressed with the necessity of using every means available to recognize syphilis early so that the individual may be given the best possible chance in life. In a previous study[1] with the Wassermann reaction before the luetin test was given us by Noguchi, it was shown how the tests compared when made in both mother and child. There were some irregularities which could not then be explained. It is highly probable that many of the irregular cases with negative Wassermann reaction, if they had been examined by means of the luetin reaction, would have been shown to be positive cases of syphilis.

In order to determine the relative value of the serum and skin reactions a systematic investigation was planned. It was hoped that the former series of cases could be examined, but as they were from the outpatient department it was not to be expected that all would be tested. In this series are included as many of the old cases as possible, other cases investigated later and on which there were more than one set of observations, and cases on which only one set of these tests was made.

The complement binding property of the serum was determined both before and after inactivation in a water bath at a temperature of 56 C. for one half hour; the technic when using the active serum was that known as the Tschernogubow modification, as outlined by Gurd, in which the natural hemolysin of human serum against guinea-pig cells constituted the hemolytic system. When using the inactivated serum the technic as originally described by Wassermann was followed rather closely. The antigen used in both instances was the acetone insoluble fraction of an alcoholic extract of a human heart.

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* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

* From the Children's Out-Patient and the Pathological Departments of Touro Infirmary, New Orleans.

1. DeBuys, L. R.: A Study of the Wassermann Reaction in Connection with Congenital Syphilis, AM. JOUR. DIS. CHILD., 1913, v, 65.

In the performance of the luetin test the technic as outlined by Noguchi was carried out minutely. Readings were made every forty-eight hours over a period of seven days and as often as possible subsequently.

The study consisted in 350 Wassermann reactions and 100 luetin tests in 175 cases. Only partial investigation could be made in twenty-four patients who did not return for complete observations. In the remaining 151 cases 321 Wassermann and 160 luetin reactions were made. Thirty former patients were included in the study. Among the former patients are considered those who were previously seen and on whom more than one set of observations were made, the period varying from one-half month to five and one half years. Nine of the luetin tests were on those already examined by the same test from one to eight months before. The later readings always corresponding to the previous ones.

There were eighty children, sixty-three mothers and eight fathers included in this investigation. Fifty-four mothers with their children, one child and his father, seven fathers and mothers and children, ten children alone, and two mothers alone. In the latter, in both instances, the Wassermann in the mother and child and the mother's luetin were the same, the child not returning for observation of the luetin reaction.

The children varied in ages from 12 days to under puberty. Forty-two were from 12 days old to under 12 months, and of these thirty-two were less than 6 months; twenty-three others were between 12 months and 7 years, the remaining being distributed from 7 years to 11 years. Seventy-four families were examined. In sixty-two families there were more than one member.

TABLE 1.—Data Concerning Patients on Whom the Wassermann and Luetin Tests Were Made

	Families	Total
Children alone	10	10
Mother alone	2	2
Mother and child	50	100
Mother and two children	8	9
Mother and four children	1	5
Father, mother and one child	5	15
Father, mother and two children	2	8
Father and child	1	2
	74	151

TABLE 2.—Results of Wassermann and Luetin Tests on Families

Wassermann			Luetin			Instances
Father	Mother	Child	Father	Mother	Child	
+	−	+	+	+	+	1
+	−	−	+	+	+	2
−	+	+	+	+	+	2
−	−	+	+	+	+	1
−	−	−	+	+	+	2
−	−	−	−	−	−	1
−	..	−	+	..	+	1
..	+	+	..	+	+	16
..	+*	+*	..	−	−	1
..	+*	−	..	−	−	2
..	+	−	..	+	+	7
..	−	+	..	+	+	4
..	−	−	..	+	+	26
..	−	−	..	−	−	4
..	−	..	..	−	..	2
..	..	+	..	..	+	1
..	..	−	..	..	+	8
..	..	−	..	..	−	1
..	..	..	..	..	..	82

* Wassermann made the same day.

TABLE 3.—Comparative Result of the Wassermann and Luetin Tests

	Wassermann	Luetin	Number
Father	+	+	2
Father	−	−	1
Father	−	+	5
Mother	+	+	21
Mother	+*	−	3
Mother	−	−	7
Mother	−	+	32
Child	+	+	25
Child	+†	−	1
Child	−	+	46
Child	−	−	8
			151

* Three Wassermann reactions made on the same day.
† Wassermann made on same day as on No. 5.

TABLE 4.—Result of Wassermann and Luetin Tests on Old Cases*

First Observation			Later Observation			No. Cases
Child	Mother	Father	Child	Mother	Father	
W+	W+	.....	W+ L+	W+ L+	.....	4
W+	W+	.....	W− L+	W− L+	W− L+	2
W+	W−	.....	W+ L+	W+ L+	.....	2
W+	W−	.....	W− L+	W− L+	W− L+	2
W+	.....	.....	W+ L+	W+ L+	.....	4
W+	.....	.....	W+ L+	W− L+	.....	1
W+	.....	.....	W− L+	W− L+	W− L+	1
W−	W−	.....	W+ L+	W− L+	.....	1
W−	W−	.....	W− L+	W− L+	W− L+	1
W− L+	W− L+	.....	W− L+	W− L+	W− L+	1
W−	.....	.....	W− L+	W+ L+	.....	1
W−	.....	.....	W− L+	W− L+	.....	7
W−	.....	.....	W− L+	.....	.....	1
W−	.....	.....	W− L−	.....	.....	1
.....	W+	.....	W− L+	W− L+	.....	1
.....	.....	.....	.....	.....	.....	30

* W signifies Wassermann, and L, luetin.

It was not possible to read the luetin tests as frequently or as long as desired in all the cases in order to determine the averages for the entire series. Many, however, did as requested, and from them the following was learned:

The shortest reaction in a baby was luetin positive in two days and negative in three days.

The latest positive reaction in a baby was on the eighth day.

The duration of reaction in a child was from two days to fourteen days.

The earliest pustular eruption in a baby was two days; latest, six days.

The shortest reaction in a mother became positive and subsided within three days.

The latest positive reaction in a mother appeared on the twenty-fourth day, close observations having been made in this case at forty-eight-hour intervals. Observations were continued because four of her children gave positive laboratory findings. In another case fourteen days elapsed before the luetin began to light up. In this instance the

mother and child gave marked Wassermann reactions and the child a pustular luetin test.

The luetin test of one mother, after an ordinary positive reaction which was persistent, on the twenty-first day became violently pustular and ruptured. The same occurred in another case on the fourteenth day. To no influencing factor could these reactions be ascribed, such as medicine.

Whether the luetin test influences subsequent Wassermann reactions we cannot say. In two children giving positive luetin reactions, in whom negative Wassermann reactions were obtained on the same day that luetin tests were made, subsequent Wassermann reactions were positive as follows:

On May 6, 1916, a Wassermann and a luetin test were made; the luetin was positive, the Wassermann, both original and Tschernogubow, was negative. On May 18, the Wassermann, both original and Tschernogubow, was again made and was positive.

In an old case on Dec. 7, 1916, the Wassermann was negative; on May 6, 1916, the Wassermann was again negative; the luetin test made on May 6 was positive. On May 20 the Wassermann, both Tschernogubow and original, was markedly positive.

The explanation of this irregularity may be either that the luetin produced a fresh outburst of toxins from the old lesions in the internal organs, thereby stimulating sufficient antibodies to produce a positive Wassermann reaction, or the small amount of dead organisms were sufficient to stimulate antibody formation in demonstrable quantities. At the present writing we have been unable to determine which is the true explanation.

In another case, however, after an interval of twelve days the second Wassermann remained the same, but the previous Wassermann and luetin were both negative.

Some mothers have complained of their children seeming to have a slight fever after the luetin tests were made. In one case, the second of the two cases just spoken of, the child on returning for observation and at the time of the positive Wassermann was not well, having had an upset which could not be explained by any physical or other laboratory examination.

In seven instances in which two luetin tests were made in the same individuals the second luetin reacted more promptly, and in five of these the second reaction was much more pronounced. The interval between the first and second luetin tests ranged from eight days to eight months. The intervals in the five pronounced second reactions were from one month to eight months. The other two were eight days and two months, respectively.

The effect of the iodids on the cases after a sufficient time had elapsed for a decidedly negative reading was negative. The iodids given in positive cases seemed to prolong their positive readings. No attempt was made to determine the effect of the administration of the iodids before the luetin tests were made. In this connection, the most violent positive luetin reactions in the series of this paper were in a mother and nursing baby in both of whom there was not the slightest evidence of syphilis. The mother, however, had some rheumatic pains, which she attributed to exposure. Needless to say, the surprise was indeed great. It developed later that the mother had been given potassium iodid in the adult service for rheumatism and was taking fifteen grains three times a day. The interesting feature in this instance was the effect of the administration of the iodids to the mother on the luetin reaction, not only in herself, but her baby. The discontinuance of the iodids caused a magic subsidence in the luetin reaction of both mother and child, and a return to the administration of the iodids to the mother produced a relighting of the luetin test in both.

WASSERMANN VERSUS LUETIN

In this study the luetin reaction appears to be vastly more reliable for determining the existence of syphilis than the Wassermann.

Table 2 shows that in the eighty-two children and parents, in all but three instances, the reading of the luetin tests was dependable, not being negative in any member of a family in which a member of the family gave a positive luetin. In the three families giving negative luetin tests with positive Wassermann reactions the following is to be said: In two instances the Wassermann reactions of the babies and the luetin tests in the babies and mothers were negative, and only the Wassermann reactions in the mothers were positive. These two Wassermann reactions were very positive and were made on the same day, but not the same day the babies' Wassermann tests were made. In the third instance the Wassermann reactions in the baby and mother were both positive and the luetin tests in both mother and baby were negative. These two Wassermann reactions were very positive and were made on the same day as were those in the other two cases just mentioned. These four constitute the only instances in this series in which the Wassermann reactions were positive and the luetin tests negative, and we believe this to be due to an error in technic and not to an error on the part of the luetin, as these all occurred on the same day and in cases that could not clinically be considered syhpilitic. Attempts to secure control Wassermann reactions were unsuccessful.

In the remaining seventy-nine instances the reading of the luetin in the child was a reliable guide to the existence or nonexistence of syphilis in the family. In none of these cases was a negative luetin

found in either parent if a positive luetin was found in the child, and with the exception of three instances looked on as errors, a negative luetin in the child was not found in any instance with a positive Wassermann in the child or with either a positive Wassermann or luetin in either parent, or brother or sister.

In the parents, whenever there existed positive Wassermann reactions, there were found positive luetin reactions, and in many instances in which there were negative Wassermann reactions there were found positive luetin reactions.

It is interesting that the luetin reactions ran uniformly in families. Either they were all positive or all negative.

In Table 3 the comparison of the Wassermann and luetin reactions is shown in the individuals. The more accurate reading of the luetin test is again evident. The same four exceptions appear in this tabulation.

Table 4 shows the old cases. These old cases had been previously studied with the Wassermann only, except in one instance. Had these cases been formerly studied by only the Wassermann in the child alone, thirteen cases out of twenty-nine would not have been recognized.

In the eight instances in which the former Wassermann reactions in the mothers were negative had no other observations been made, in all of them syphilis would have been excluded.

The Wassermann reaction may vary from time to time owing to the activity or inactivity of syphilis in the individual. In six instances in the child the former and later reaction were positive on one occasion and negative on the other. And in eleven instances the Wassermann reactions were negative on both examinations in the child and the luetin reaction gave positive findings, not only in the child on one occasion, but in one or both parents in the remaining ten instances.

In every instance in which the Wassermann was positive in either the mother or child the luetin reaction was invariably positive, not only in the child, but also in all the parents tested.

CONCLUSIONS

1. The Wassermann reaction is not so valuable as the luetin test in cases of hereditary syphilis.

2. Our series shows that it is impossible for a mother to give birth to a child who gives positive laboratory tests for congenital syphilis without herself giving positive tests.

3. While we believe that the luetin test is of more value in being more often positive than the Wassermann, we do not believe that it should displace the Wassermann, as both tests, it would seem, serve distinct purposes, the Wassermann to give evidence of the presence of

antibodies in the circulation, indicating an active process; while the luetin not only gives this evidence, but also indicates an existing syphilitic condition, even though it be inactive.

4. The luetin test is not without its disadvantages, as it requires considerable experience in differentiating the lesion from the simple reaction produced by the intradermal injection of sterile inert foreign material. It is also influenced by the administration of certain drugs, which may give rise to a pseudoreaction, thereby adding to the possible inaccuracy in the interpretation of its reading.

5. Luetin reactions should not be considered negative until sufficient time shall have elapsed to warrant such a reading.

Our sincerest thanks are due Dr. Hideyo Noguchi for supplying us with luetin for this study, and to Drs. J. F. Baldwin and Ruffin T. Perkins for their valued assistance.

TREATMENT OF HEREDITARY SYPHILIS*

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The status of the treatment of hereditary syphilis is today not wholly unlike that of adult syphilis. Up to seven or eight years ago mercury and its salts and potassium iodid had for four hundred years or more done fairly well in all except the very severe cases, in which the patient died. The "cure," as they called it then, or the disappearance of symptoms and visible lesions was slow, often requiring months and years. The perfection of the Wassermann reaction and its intelligent application to treatment, as well as to diagnosis, gradually broadened our conceptions as to the problems of the disease and brought sharp realization that our clinical cures were so in name only and that far longer periods of treatment and observation were necessary. This sane attitude was greatly influenced by the widely heralded appearance of the patented arsenical preparations. Here was the long-sought-for cure, short, safe and easy, with little bother to parent or doctor, one or two injections only and the child was well! These articles were received and used with enthusiasm only slightly tempered with caution. The literature immediately blossomed, in fact became all cluttered up, with glowing reports of cures based on a few patients treated by one or two doses or observed for only a short time. There were deaths, to be sure, but very few of them could be traced directly to the disease or the cure. Gradually, however, it was noticed that the cured patients did not stay cured and that clinical relapses followed as a rule the cessation of treatment.

The war put a stop to the importation of arsenicals and made us look around for other forms of treatment. It also gave us an opportunity to take a long breath and review the accumulated experience in a saner mood, digest it and apply the results to our cases with caution and common sense. The general feeling today is that the arsenicals, while producing almost miraculous immediate results, do not cure, and that successful treatment, far from being short and simple, is long and complicated and depends on the intelligent application of a combination of drugs to the type of case treated.

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*From the medical service of the Children's Hospital, Boston.

With the new light thrown on pathologic conditions by the Wassermann reaction it has become convenient to divide for the purpose of treatment congenital or hereditary syphilis into the following four types:

1. Fetal, that is, intra-uterine.

2. Early infantile, secondary, or inflammatory, in which the lesions are largely mucocutaneous and visceral, frequently osseous, and occasionally nervous, occurring through the first year of life.

3. Tardy, late, tertiary, or hypertrophic, in which the lesions are largely osseous, nervous and gummatous.

4. Latent, in which the only direct evidence of syphilis is a positive Wassermann reaction.

The second and the third type overlap considerably and may have several sets of lesions in common.

TREATMENT

Fetal.—Common sense would indicate that a pregnant syphilitic woman would have a better chance of giving birth to a viable child if she were effectively treated than if untreated. While little has been written on this phase in this country, I know that it is the custom in Boston and other cities which have pregnancy—or prenatal-care—clinics to treat pregnant syphilitic women; that the general feeling is that the treatment does no harm, that the mothers are very much benefited, that there are fewer pregnancies terminated by abortion or stillbirth, and that the percentages of viable children are greater. Abroad Meyer[1] and others[2] have treated numbers of pregnant syphilitics and have concluded that vigorous treatment does the mother no harm and increases tremendously the percentage of viable children born. In Boston Huntington[3] tells me that every pregnant woman coming into the pregnancy clinic of the Boston Lying-In Hospital is required to have a Wassermann test. All showing a positive reaction are referred to the Massachusetts General Hospital for active antispecific treatment. He states positively—but is not in a position to give figures—that not only is the percentage of viable children very much increased, but that very few new-born children of treated syphilitic mothers show manifestations of syphilis. Williams[4] and others[5] show that the greatest single influence in fetal mortality is syphilis,

1. Meyer, E.: München. med. Wchnschr., Aug. 18, 1914, lxi, 1801.

2. Sauvage: Quoted by E. Meyer (see Footnote 1). Fabre and Bourret: Lyon méd., 1912, cxix, 716. Galliot: Arch. de méd. d. enfants, 1913, xvi, 892. Findlay and Robertson: Quart. Jour. Med., 1915, viii, 175.

3. Huntington, J. L.: Personal communication to the author.

4. Williams: Tr. Am. Soc. Prev. of inft. Mort., p. 46.

5. Jeans and Butler: Am. Jour. Dis. Child., 1914, viii, 327.

estimating that from 26 to 40 per cent. of all fetal accidents are due to that cause alone and recommending the earliest possible active maternal antisyphilitic treatment. Others,[6] however, while writing in much the same vein, believe that maternal treatment should be undertaken with caution and cite instance of severe fetal accidents apparently due to maternal treatment.

Early Direct Treatment.—Experience has shown that inasmuch as the Wassermann reaction is negative at birth in so many children of known syphilitic parentage,[7] clinical evidence should override the negative Wassermann in the new-born and treatment be instituted at once.[8] Owing to difficult and complicated technic as well as to reported serious by-effects, salvarsan has largely been discarded, except in very small doses.[7] The feeling is now general that neosalvarsan, owing to ease of administration, simple technic and lack of harmful by-effects, is preferable to salvarsan, but that its effect is not so impressive or so lasting. Further, most of the observers[9] conclude that none of the arsenicals alone cure, even with prolonged and frequent use; that while clinical evidence disappears almost magically and remains in abeyance as long as arsenic is administered, yet in only a few weeks after cessation of arsenic, symptoms again become manifest. These observations and the scarcity of salvarsan and neosalvarsan, as well as the lack of adequate experience with the new American arsenicals, diarsenol and arsenobenzol, have led to a reaction favoring the old treatment by mercury and the feeling that arsenic is useful at first and in acute phases, but alone is insufficient, that it must be accompanied by mercury in some form. Some[10] believe that mercury first, for a short time, prepares the way for an intensified action by arsenic and diminishes its dangers. Recent opinion seems to favor mercury by inunction, or mercury with chalk over other mercurial preparations and the inunctions appear to be more popular than the mercury with chalk.

The question of the dose of salvarsan or neosalvarsan has been pretty well threshed out without definite decision, some claiming that the dose of from 0.01 to 0.015 gm. salvarsan, or from 0.015 to 0.02 gm. neosalvarsan per kilogram body weight is too small to give the best effect, and lay clinical failures to the smallness of the dose. Others feel that the dose is too large and fraught with danger, but not very effective. Most[11] agree, however, that the dose should be given in concen-

6. Lemeland and Brisson: Arch. mens. d'obst. et de gynéc., Paris, 1913, cxiii, 256. Dupérie: Gaz. hebd. d. sc. méd. de Bordeaux, 1913, xxxiv, 87.
7. Bunch: Brit. Jour. Child. Dis., 1914, xi, 297.
8. Steinert and Flusser: Arch. f. Kinderh., 1915, lxv, 45.
9. Dunzelman: Ztschr. f. Kinderh., 1913, v, 512.
10. Hoffman: Dermat. Ztschr., 1914, p. 508.
11. Blechman: Paris médical, 1913-1914, xiii, 205. Holt and Brown: Am. Jour. Dis. Child., 1913, vi, 174.

trated solutions intravenously at any accessible vein, the veins of the neck or scalp being most favored. In cases in which the veins are so small or for other reasons attempt at intravenous medication seems inadvisable, injections through the longitudinal sinus according to the method of Marfan and Helmholtz[12] is ridiculously easy. The ingenious head-holder which Helmholtz has designed has in our experience proved unnecessary.

Most observers agree that the arsenicals should be supplemented by mercury in some form, such as inunctions, mercury with chalk, mercurous chlorid, mercuric chlorid, and mercurous salicylate by mouth or by intramuscular injection. One of the most experienced[13] favors topical applications of mercuric chlorid to the moist lesions while neosalvarsan is being administered and gives 2 mg. of mercuric chlorid intramuscularly once a week following. Another[14] gives twelve injections of mercurous chlorid 0.001 gm. per kilogram followed by eight doses of neosalvarsan 0.015 per kilogram, followed by twelve doses of mercurous chlorid again. He also replaces at will the mercurous chlorid by inunctions of mercury. He believes that this series of treatment should be repeated every few months. Others[15] prefer mercury with chalk to supplement the arsenicals, in doses of one-half to one and one-half grains three times daily for from two to six weeks, then omitting for from one to three weeks and repeating.

As to arsenicals other than salvarsan and neosalvarsan, diarsenol (Canadian salvarsan) has apparently been used but little among children; what experience is available from its use among adults would place it parallel with salvarsan, except that it is liable to become decomposed more readily, causing disquieting by-effects,[16] and is recommended to be used in doses slightly smaller than salvarsan. Arsenobenzol, introduced by Schamberg, is similar to salvarsan. Dr. Schamberg[17] states that he gives from 10.0 to 15.0 mg. in 1.25 c.c. sterilized liquid petrolatum containing a drop or two of beechwood creosote. He advocates from 4 to 6 mg. per kilogram body weight. He injects deeply into the gluteal muscles, and states that the injection causes very little pain. He reports satisfactory results. This method apparently presents at least the advantage of simplicity over the complicated technic of the salvarsan type of intravenous administration. Salvarsan sodium or

12. Helmholtz: Am. Jour. Dis. Child., 1915, x, 194.
13. Baginsky: Therap. d. Gegenw., 1915, lxvi, 67.
14. Mueller: Berl. klin. Wchnschr., 1915, lii, 1034.
15. Veeder and Jeans: Am. Jour. Dis. Child., 1916, xi, 177. Smith: Boston Med. and Surg. Jour., 1916, clxxxiv, 198. Cook: Jour. Am. Med. Assn., 1916, lxvi, 865.
16. Ormsby and Mitchell: Jour. Am. Med. Assn., 1916, lxvi, 867.
17. Schamberg: Personal communication to the author; also Jour. Am. Med. Assn., 1915, lxv, 1387.

salvarsan natrium,[18] as recently advocated for adults, is as simple to administer as neosalvarsan. I find no record of its use among children.

In addition to the above, there are certain startling, really new, ideas, such as the use of antimony,[19] quinin,[20] tuberculin,[21] to induce fever, and an unusual but not necessarily valuable contribution is that of administering mercury vapor by inhalation.[22]

Indirect Treatment.—Practically all observers agree that most syphilitic babies get along better when receiving their mother's milk than when artificially fed. A good deal has been said, much has been done, but very little proof has been adduced that breast milk alone from a treated syphilitic mother materially influences the lesions in her nursling. Arsenic or mercury has been found in such breast milk in only minute traces by one or two observers,[23] but Ehrlich himself believes the benefit following this method to be due to the excretions of antibodies in the milk, these having been set free in the mother by the destruction of the spirochetes; but he says the effect on the child is uncertain. Others feel that the effect lies wholly in the better quality of the milk owing to the improved general condition of the mother. Salvarsanized serum[24] has been injected by some, but with unsatisfactory results.

Briefly, then, a hypothetical patient would receive the following treatment:

First, during pregnancy its mother would be treated vigorously.

Second, at birth, whether showing lesions or not, or whether having a positive Wassermann reaction or not, it would receive inunctions of 25 per cent. mercurial ointment for about two weeks, during which time, if lesions occurred, or if the patient got worse, it would immediately receive 0.15 or 0.2 gm. neosalvarsan in 5 c.c. distilled water, intravenously, at weekly intervals, meanwhile continuing the mercury. As soon as the lesions disappeared the neosalvarsan would be stopped and the mercury alone would be continued for several months, except for temporary cessation made advisable by the appearance of a mercurial diarrhea. At six months a Wassermann test would be made, and if positive, mercury would be continued as above. If negative, mercury should be given intermittently about half the time, that is to say, every other week or every other fortnight, but should not be omitted for

18. Wechselman and Dreyfus: Müenchen. med Wchnschr., 1915, lxii, 6.
19. Brandweiner: Wein klin. Wchnschr., 1916, xxix, 26.
20. Breitman: Therap. Monatsh., 1914, xxviii, 504.
21. Biack: Wien. klin. Wchnschr., 1915, xxviii, 49. Luithlen: Ibid., 1915, xxviii, 1421.
22. Frankensein: Deutsch. med Wchnschr., May 13, 1915, No. 20; abstr. Jour. Am. Med. Assn., 1915, lxv, 60.
23. Simpson and Thatcher: Brit. Med. Jour., 1913, ii, 534.
24. Meirowsky and Hartman: Quoted by Simpson and Thatcher in quoting Jeanselme (Footnote 23).

longer than a fortnight. At 1½ years a Wassermann test should be made, but the result should have no influence on the treatment. At 2 years treatment may be stopped if the Wassermann reaction is then negative, and if again negative at 2½ years the patient may be considered tentatively cured. Many believe,[25] however, that the Wassermann should be made more frequently and over a longer period than this. Others believe that neosalvarsan or some other arsenical should be given every two, three, or four months. Many believe that an apparently cured patient should be kept under observation for several years and a Wassermann test made at intervals of from six months to a year.

Treatment of Tardy, or Late, Types.—To a certain extent, manifestations of early and of late syphilis overlap. As a matter of fact, there is no clear-cut distinction in the lesions other than the time of their appearance; that is to say, some early cases present manifestations more often seen in later syphilis, and, conversely, some late cases present lesions usually seen in the early stage. For example, many bone lesions are seen very early; occasionally lesions of the nervous system are seen very early, and conversely. Ordinarily late cases may be divided into two groups, the first presenting lesions in bones, joints, eyes and teeth, developing gummatas, and producing general malnutrition, that is, corresponding pretty closely to what we used to call the tertiary stage of adult syphilis. It appears to be the feeling that late or tardy syphilis represents an essentially mild infection, or the results of an insufficiently treated earlier stage, in which results of treatment are more encouraging than in the adult, but less so than in the early stage, and it seems also that the arsenicals are not so urgently needed, but that patients do better with them than on mercury alone.[26] This feeling is not borne out by our experience at the Children's Hospital. The second group represents lesions of the central nervous system. In cases of early cerebral involvement corresponding to what we call syphilitic meningitis and encephalitis, hydrocephalus, usually accompanying mucocutaneous lesions, mercury and potassium iodid were held to be pretty ineffective. But treated as cases of ordinary early syphilis, that is to say, with arsenic and mercury, the lesions clear up fairly rapidly. While the truly late cases of cerebral involvement, idiocy, epilepsy, late hydrocephalus, paralysis, etc., are possibly more responsive to treatment than corresponding adult cases, yet they are susceptible to only little improvement, whether treated along the later lines or treated for acute general syphilis.[27]

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25. Boardman: Jour. Cutan. Dis., 1914, xxxii, 545.

26. Yerington and Holsclaw: Am. Jour. Dis. Child., 1914, vii, 32. Strathy and Campbell: Ibid., 1913, vi, 187. See also Footnote 15.

27. Jeans, P. C.: Personal communication to the author.

While little has yet been published on this particular phase, some feel that experience with adults would lead to the belief that direct treatment of the nervous system by the Swift-Ellis technic, or other intraspinous application, would have positive results. Others[28] conclude that patients not responding to intravenous or other general treatment are not benefited by intraspinous treatment. Walker,[29] however, reports among other cases, that of a child of 3 years with syphilitic meningitis, who received no benefit from general antisyphilitic treatment. He was then given in all four doses of salvarsan, 0.2 gm., and also nine intraspinous injections of salvarsanized serum, undiluted, and mercurial inunctions, following which blood and spinal fluids became negative and cell counts normal. After four months the child was apparently normal, except for deafness.

Again, Leopold[30] cites three patients with late syphilis, with manifestations in bone, viscera and central nervous system, distinctly improved as to mental condition following intensive treatment by arsenic and mercury. One patient received a dose of salvarsanized serum intraspinously. Post[31] tells me that he believes patients with syphilis even of the central nervous system, are improved by general treatment with arsenic and mercury.

Latent Syphilis.—Strictly speaking, latent syphilis is syphilis in which the only manifestation is a positive Wassermann reaction. Nevertheless, the Wassermann test has brought us to the conclusion that many cases of backwardness, malnutrition, underdevelopment and mental retardation, presenting no lesions whatever of syphilis, are really cases of syphilis in which the infection has never gotten under way. Such cases are usually in older children, not necessarily sick, but distinctly under par in one or several ways. The spleen is not necessarily enlarged, although it often is so. A careful and tactfully taken history will bring up a strong probability of parental syphilis. The Wassermann reaction is positive, justifying the routine employment of this reaction in all cases in which the condition is not ordinarily satisfactorily explained.[32]

Surprisingly little has been done here or abroad in the study or treatment of this condition. Common sense would indicate that treatment is advisable, and experience would justify the belief that one or several doses of arsenic might produce a provocative reaction[33] or

28. McIntosh, Fildes, Head and Fearnsides: Brain, No. 36, p. 1. Fildes and McIntosh: Ibid., p. 236.
29. Walker, I. C.: Boston Med. and Surg. Jour., 1916, clxxiv, 195.
30. Leopold, Jerome Sam: Personal communication to the author.
31. Post, Abner: Personal communication to the author.
32. Post, Abner: Boston Med. and Surg. Jour., 1914, clxx, 11.
33. See Footnote 26, second reference.

mobilize the spirochetes and bring them within the reach of further treatment.[34]

Dangers of Treatment.

1. Of mercury. In a gathering of this sort little need be said about the untoward effect of the excessive or too long use of mercury. Outside it still seems to be very little realized that salivation and gingivitis occur only in the presence of teeth, and that the symptom most to be watched for is a diarrhea not accounted for by the child's feeding or by its general condition.

2. Arsenic. Very few cases of evil effects directly attributable to arsenic have been reported lately. Most of the so-called "salvarsan deaths" were due to hemorrhagic encephalitis and nephritis. It is believed that many of the severe reactions are caused not so much by the arsenic as by the endogenous toxins liberated by so many dead spirochetes. The less serious by-effects are vomiting, fever and bloody

34. The following references are not directly quoted in this paper, but they will be found of value for the purpose of weighing evidence or of indicating the balance of opinion:

Jeans: Familial Syphilis, Am. Jour. Dis. Child., 1916, xi, 11.
Neff, F. C.: Mo. State Med. Assn. Jour., St. Louis, xii, 338.
La Fetra: New York State Jour. Med., 1916, xvi, 3.
Steiner: Med. Rec., New York, April 24, 1915, lxxxvii, 705.
Rostenberg: Med. Rec., New York, 1915, lxxxvii, 9.
Ogilvie: Jour. Am. Med. Assn., Nov. 28, 1914, lxiii, 1936.
Heidingsfeld: Ohio State Med. Jour., 1914, x, 11.
Findlay and Robertson: Glasgow Med. Jour., 1914, lxxxii, 6.
Elias: South. Med. Jour., 1914, vii, 708.
Schamberg, J. F.: Jour. Am. Med. Assn.
Corbus: Illinois Med. Jour., 1914, xxvi, 2.
Fildes and McIntosh: Brain, No. 37, p. 191.
Andronescu: Deutsch. med. Wchnschr., 1912, xxxviii, 761.
La Fetra: Arch. Pediat., 1912, xxix, 654.
Von Bokay: Wein. klin. Wchnschr., 1911, xxiv, 583; Arch. f. Kinderh., 1913, lx, lxi.
Baginsky: Festschrift, p. 107.
Wechselmann: München. med. Wchnschr., 1915, lxii, 1638.
Best: Med. Rec., New York., 1916, lxxxix, No. 11, p. 473.
Rytina and Judd: Am. Jour. Med. Sc., 1915, cxlix, 2.
Wolf: New York State Jour. Med., 1916, xvi, 1.
Thompson: Jour. Am. Med. Assn., 1915, lxiv, 18.
Mott: Brit. Med. Jour., Jan. 30, 1915.
Pedersen: New York Med. Jour., 1915, ci, 2.
Corbus: Jour. Am. Med. Assn., 1914, p. 550.
Fordyce: Jour. Am. Med. Jour., 1914, p. 552.
Riggs: Jour. Am. Med. Assn., 1915, p. 840.
Swift: Jour. Am. Med. Assn., 1915, p. 209.
Hoffman: Deutsch. med. Wchnschr., 1914, xl, 1168.
Werther: Deutsch. med. Wchnschr., 1914, xl, 1099.
Schmitt: München. med. Wchnschr., 1914, lxi, 1337, 1396.
Saphier: Wien. klin. Wchnschr., 1914, xxvii, 1058.
Krefting: Deutsch. Med. Wchnschr., 1915, xli, 979.

diarrhea. I was impressed in going over the literature as to the salvarsan deaths with the large number of patients reported as dying of pneumonia two or three weeks following salvarsan treatment. It seems to be the general feeling that arsenic should not be used in cases of nephritis or of cardiac disturbance.

In the Children's Hospital in Boston we have treated a few over one hundred patients with hereditary syphilis in the last two years. Of these, fifty-eight have now developed enough clinical evidence to be of value. We have naturally treated no fetal patients. Of the second, or early type, we have treated fifty patients, most of them coming in when under 6 months old; of these, eighteen, presenting clinical evidence of early syphilis, positive Wassermann reaction, but not seeming acutely sick, received mercury alone, thirteen by inunction, five receiving mercury with chalk. None died and all did fairly well, were clinically free from signs in from two to six months (none under two months), and only two now have a negative Wassermann. These have been treated for over a year and a half. All who have been treated for more than six months seem to be as healthy as the average baby. At first we treated all patients with neosalvarsan, but as the drug became scarce and costly we reserved it for use on those who were very sick and who we felt would die within a few days on mercury alone. Of the seventeen patients so treated only four died, one two days, one five days and two between two and three weeks after treatment, who did not return to the hospital as directed. These latter two deaths were apparently from bronchopneumonia. The remaining thirteen of these seventeen desperately sick babies are now, after a period of months, as well as the average baby. Only eight of them, however, have a negative Wassermann; only one of these eight has been treated for less than six months. Nine other patients not desperately sick were treated by neosalvarsan and mercury. In them the effect of the neosalvarsan was even more rapid than in the desperately sick children in causing the disappearance of mucocutaneous lesions. Of those nine, seven, now treated for nearly two years, have had two negative Wassermann tests three months apart.

Our maximum dose of neosalvarsan has been 0.4 gm. in babies of 1½ years or over. At 1 month or under we give 0.1 gm.; from 1 to 6 months, 0.2 gm.; from 6 months to a year, 0.25 gm., and from 1 year to 1½ years, 0.25 to 0.35 gm. We give the neosalvarsan intravenously in 5 c.c. freshly distilled water, and repeat the dose weekly until all evidence of syphilis except the Wassermann reaction has disappeared. In all cases in which it has been possible the baby has been breast fed and the nursing mother has received treatment

at other hospitals. Our largest number of injections of neosalvarsan was seven, in which case the dose was from 0.05 to 0.075 gm., which I believe to be altogether too small. There were five patients, however, who received only one dose, varying from 0.1 to 0.2 gm., and they presented no visible lesions except pigmentation at the end of from three to seven days. All the patients receiving neosalvarsan were started on mercury on the same day. Most of the patients receiving neosalvarsan were clinically well within one month.

A word as to prognosis in this type of case. Our experience does not justify the pessimistic attitude of Veeder and Jeans and others who report an ultimate mortality of about 40 per cent. and a morbidity of about 60 per cent. Our immediate deaths were four; our ultimate deaths have been none. Our morbidity, in patients treated long enough to count, is practically nil. These children are not even backward and are a fine-looking lot of babies. This is quite in contrast with a series of twenty consecutive patients admitted to our hospital wards and treated before the advent of arsenic. These were necessarily severe cases. Of these twenty patients with severe syphilis, sixteen died within two months, one is living and three cannot be found.

Of the late type of case, we have treated eight patients, varying from 4½ to 9 years old. Four, who were treated with mercury and potassium iodid, showed some improvement and all have positive Wassermann after periods of treatment of from six months to two years. Four have been treated by neosalvarsan and mercury and have improved tremendously in general physical condition within a month after receiving neosalvarsan, but still have a positive Wassermann and the mental condition has failed to reach normal, although considerably improved. We feel that neosalvarsan, while not wholly effective in this condition yet offers more hope of improvement than the older remedies. We have used no intraspinous medication, believing that the nerve men were more qualified than we to carry out this procedure.

Latent Cases.—We have to date treated only five cases corresponding to the latent type. (These are not included in the fifty-eight cases reported above.) Four of these have received neosalvarsan as well as mercury. Their mothers say they are brighter, "do not act so queer" and are much livelier. All of them have gained more rapidly in weight than before treatment was undertaken. The one receiving mercury alone has also improved and gained in weight. They have, however, been under observation and treatment for too short a time to present evidence of value.

CONCLUSIONS

1. Fetal syphilis should be treated by treating the pregnant syphilitic mother vigorously. The balance of evidence shows that the child is much benefited thereby.

2. Arsenic should be used in fairly large doses if immediate intense action is desired.

3. Mercury in one form or another should be used in conjunction with arsenic and continued a long time after all evidence of the disease has disappeared.

4. Treatment should be persisted in for at least two years, after which a negative Wassermann, after six months without treatment, may be considered evidence of a cure.

5. Neosalvarsan appears to be the most favored arsenical.

6. Lesions other than of the central nervous system may be readily relieved.

7. To date the therapy of the lesions of the central nervous system is disappointing but not discouraging.

8. Latent cases should be treated.

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PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD*

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Since the last Review slight advances have been made here and there but, as a whole, our conception of syphilis has been changed but little. The same questions are debated and the same conflict of opinion is manifest. It is not the purpose of this review to notice every article published, but rather only so many as will serve to demonstrate efficiently the trend of present thought. Nevertheless, the general plan of the previous review has been adopted without other alteration.

SOLUTIONS FOR INJECTIONS

On the whole, the ancient methods of preparing the arsenical remedies for injection still prevail. The only noteworthy modification is Taege's[1] method of procuring an absolutely sterile salt solution. He first rids the water of any calcium, magnesium, manganese or iron which it may contain by adding an alkali, allowing the mixture to stand twenty-four hours and then filtering. The glass or crockery vessel to be used is scrubbed out with strong hydrochloric acid. Then a mixture of 2.5 gm. strong, hydrochloric acid and 1 gm. sodium chlorid is poured in. Next, a 1 per cent. alcoholic solution of phenolphthalein and a solution of sodium chlorid are added, drop by drop, until a distinctly pink color is produced. A sterile normal salt solution results which will keep for months without change, uncovered. The salvarsan can be dissolved easily in the acid solution and later can be neutralized, avoiding, however, overalkalization in the process.

THE THERAPY OF SYPHILIS

Passing to the consideration of the therapy of syphilis, we shall find no such comparative agreement. The dosage, the therapeutic indications and the method continue to be much disputed.

Dreyfus[2] advises the employment of salvarsan in from 1 to 1.5 per cent. solution.

* Submitted for publication June 7, 1916.

1. Taege: München. med. Wchnschr., lxi, 1325.
2. Dreyfus: Deutsch. med. Wchnschr., lxii, 178.

Schmitt* advocates, by implication, concentrated solutions. He says that according to the evidence there is danger in submitting a diseased circulatory apparatus to the sudden strain of the dilute solution with its consequent increase in the bulk of the circulating medium.

Simon[3] recommends the cautious administration of small doses of salvarsan in old syphilis, incompletely or carelessly treated with large doses at some previous time, in cases of secondary syphilis, and in cases in which meningitis has been demonstrated by lumbar puncture. Otherwise a troublesome and even fatal Herxheimer reaction may be excited. He reports a case in which the reaction caused a fatal edema of the glottis. Simon says 0.2 gm. is an average primary dose for adult patients. If the temperature or the spinal fluid shows no ill effects, subsequent doses may be gradually but cautiously increased.

Nicholas and Mutot[4] agree with Simon that the initial dose of salvarsan should be small and that subsequent doses should be increased gradually and cautiously. They calculate the normal dose on the basis of 0.01 gm. salvarsan, or of 0.015 gm. neosalvarsan, to each kilogram of body weight. The maximum dose of salvarsan however, should not exceed 0.6 gm. and of neosalvarsan, 0.9 gm. Two courses of five or six injections each, one injection each week, may be employed, the second course commencing one or two months after the first.

Leir's[5] abortive method consists of the combined use of neosalvarsan and of a soluble mercurial salt. He first injects the mercurial and, a little later, the neosalvarsan. This preliminary treatment is followed by weekly injections of neosalvarsan for five or six weeks, and by about twenty injections of mercury salicylate at two or three day intervals. If possible the primary sore is excised or at least cauterized. In secondary syphilis he advocates weekly injections of from ½ to 1 per cent. suspensions of mercury salicylate or, if the tonsils show signs of recurring disease, of the bichlorid or succinamid.

Krefting[6] believes in large doses of salvarsan. Three to five injections, he says, given at intervals of two weeks, will cure primary syphilis. In secondary syphilis eight to fifteen doses may be required. No rule of treatment can be formulated, however, save that it must not stop with the production of a negative Wassermann. In his opinion salvarsan therapy has no contraindications.

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* Footnote 10.

3. Simon: Canad. Pract., xxxix, 655.
4. Nicholas and Mutot: Ann. de dermat. et de syph., 1914, Series 5, iv, 391.
5. Leir: München. med. Wchnschr., 1914, lxi, 2333.
6. Krefting: Deutsch. med. Wchnschr., 1915, xli, 979.
7. Hell: Deutsch. med. Wchnschr., 1915, xli, 787.

Hell[7] is convinced that the most efficient method of treating congenital syphilis is by combining inunctions or intramuscular injections of mercury with intravenous injections of salvarsan. He insists, however, that it is important to add to this treatment hygiene and breast milk feedings. He uses either daily inunctions of mercury for from four to six weeks, with a bath after every sixth treatment, or biweekly injections of from 0.003 gm. to 0.005 gm. of the bichlorid (mercuric chlorid 1, sodium chlorid 10, distilled water 100). The mercurial course is followed by a series of four or five weekly intragluteal or intravenous (into the temporal vein) injections of from 0.005 gm. to 0.15 gm. of neosalvarsan in concentrated solution. A second combined course is given a few months later, succeeded, perhaps, by a third or even by a fourth. Hell never gives salvarsan by intramuscular injection because of the danger of necrosis.

Leir[5] reports that all patients treated solely with mercury had recurrence.

According to de Aja[8] neosalvarsan in small doses is beneficial in many cases in which it was once supposed to be contraindicated; for instance, in hereditary syphilis, in nerve syphilis, in aortitis and aneurysm with cardiac compensation and, often, in renal disease. Nevertheless, he concludes neosalvarsan can not safely be prescribed, indiscriminately by every one or for every one.

Wechselmann,[9] too, says that nephritis is no bar to arsenotherapy, provided only that the kidneys are functionally active. If albuminuria is present, he would advise a primary course of intrafascial injections of neosalvarsan before administering it intravenously.

Schmitt's[10] deductions, drawn from an analysis of von Mentberger's[11] book, are that in certain directions arsenotherapy demands care. Patients with circulatory or other grave diseases should be treated cautiously and never in the ambulatorium. The salvarsan solution should be alkaline, as acid solutions predispose to embolism of the lungs. Hepatic complications, even if no more than the passive congestion of heart disease, require especial caution. Too large dosage or too frequently repeated injections may cause fatal renal damage. In the presence of already irritated or crippled kidneys, salvarsan should not be given. The possibility must be remembered that a local Herxheimer reaction may cause a disseminated miliary tuberculosis by its effect on a preexisting, localized focus or produce dangerous symptoms in malignant tumors seated over vital parts. In nerve syphilis salvarsan must be administered early and in repeated,

8. De Aja: Actas Dermo-Sif., 1915, vi, 1.
9. Wechselmann: Deutsch. med. Wchnschr., 1916, xlii, 178.
10. Schmitt: München. med. Wchnschr., 1914, lxi, 1337.
11. Metberger: Two Hundred and Seventy-Four Deaths from Salvarsan.

fractional dosage. It must not be used if meningitis exists. Salvarsan and mercury may be used in combination.

On the other hand, Wechselmann[9] says that salvarsan and mercury should not be combined, as the result is harmful in at least 50 per cent. of the cases. Fischer,[12] likewise, says that the administration of mercury after preceding salvarsan injections may cause death.

SALVARSAN ACCIDENTS

Simon[13] says that every active antisyphilitic remedy is liable to excite a serious Herxheimer reaction. Schmitt, already quoted, says that salvarsan accidents are due, in larger part, not to the mercury used in combination, but to toxemias produced by overdosage. A smaller part is to be explained by personal idiosyncrasy. The danger is especially great in nerve syphilis for, unquestionably, neurorecurrences have increased with the use of salvarsan and in spite of every effort to avoid them. Fordyce[14] writes that intensive salvarsan treatment which does not cure tends to promote the development of a state of anaphylaxis and to increase the liability to severe, local manifestations. The late vascular symptoms he attributes to a state of allergy, but questions the theory that nerve syphilis is an anaphylactic phenomenon. He is inclined to believe that it is due to the extension of a primary, meningeal process, seated on the posterior roots between the ganglia and the cord, which causes a degeneration of the afferent fibers and eventually an ascending tract degeneration in the cord. Nicholas and Mutot[4] found that serious complications, even coma and death, were more frequent after salvarsan therapy, especially if the solution was acid. To the best of their observation, the primary administration of mercury does not lessen liability to salvarsan accidents. Schmitt[10] could find no satisfactory explanation of the part played by salvarsan in the production of fatal metabolic disturbances, or of fatal results in cases of status thymicolymphaticus or of diabetes. He also found no explanation for the large number of cases which develop signs of meningeal irritation, epileptiform attacks or coma after salvarsan. Many alleged salvarsan deaths, Schmidt decided, had no foundation in fact. Fischer[12] would require a necropsy record to be submitted in proof with every claim of death by salvarsan. As regards fatal encephalitis hemorrhagica, in 6,000 necropsies, he rarely encountered a case which could, with justice, be laid at the door of salvarsan.

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12. Fischer: Deutsch. med. Wchnschr., 1915, xli, 908.
13. Simon: Canad. Pract., 1914, xxxix, 655.
14. Fordyce: Am. Jour. Med. Sc., 1915, cxlix, 761.

WHY EFFICIENCY VARIES

Takahashi* studied, experimentally, the fate of salvarsan in the tissues. His conclusions were as follows:

1. Salvarsan produces an extensive necrosis of all tissues at the site of its injection. Regurgitation, in animals, occurs, in about 350 days, by a preliminary process of acute inflammation. Fourteen days after the injection, a leukocytic infiltration walls off the injected mass. Gradually the necrotic process is replaced by the granulation tissue of chronic inflammation growing inward from the periphery.

2. The elimination of the injected, insoluble salvarsan has three reactive stages. The primary stage is of necrosis, in which the lymphatics carry away a certain amount. In the succeeding, second stage, the walled-in foreign substance is changed into collections of coarse, opaque globules, which can be dissolved with difficulty. If an abscess forms, some globules are discharged with the pus. In the third stage giant cells invade the remaining mass and take it up. In man such regenerative processes require not less than 400 days.

Stühmer[15] endeavored to trace the injected substances in the tissues by means of a color reaction. Rabbits were used for the experiment. He concluded that neosalvarsan was the most evenly distributed substance and alkaline solutions of salvarsan a close second. Salvarsan, in acid solution, was most abundant in the lung tissue, which seemed to filter it out. Concentrated alkaline solutions were similarly filtered. Concentrated neosalvarsan solutions, on the other hand, distributed the drug uniformly throughout all the tissues of the body. Infiltrations occurred in lung, liver and spleen, rapidly and equally. Storage depots were formed which, in the case of salvarsan, freed small amounts to the bloodstream for three days and, in the case of neosalvarsan, for about twenty-four hours. A large proportion of the salvarsan was eliminated unchanged, by way of the kidneys and the intestinal tract. The latter fact suggested that the symptoms of toxemia might be due to the oxidation of the drug in the intestine, during intestinal disturbances, with resorption of the poisonous product. Stühmer found, also, that repeated injections increased the capacity of the storage depots. Salvarsan seemed to respect the nervous system, but neosalvarsan exhibited a special affinity for the meninges. The result gives a practical hint as to the choice of a remedy in meningeal involvement.

Schümaker† discovered a new test for salvarsan in the urine. During the course of a quantitative, colorimetric urinalysis, he observed that salvarsan answered to all the classic requirements of a true dye. It was absorbed by animal charcoal. It contained (two) aromatic rings, a chromophore (a group of doubly bound atoms, in this instance,

* Takahashi: Arch. f. Dermat. u. Syph., 1914, cxx, 31.

15. Stühmer: Arch. f. Dermat. u. Syph., 1914, cxx, 698.

† Schümacher: Dermat. Wschnschr., 1914, lix, 1295.

As=As—), and auxochrome groups (which can form salts). Therefore, both physically and chemically salvarsan must be considered a true dye.

The discovery furnishes fresh confirmation of Wassermann's theory that the therapeutic activity of remedies composed of combinations of dye stuffs and poisons is due to the ability of the dye to lead the poison to the diseased cells. This action occurs, however, only when the poison is an essential part of the dye, and not merely an addition to it which can be easily split off. For example, in toluolazo, mercury, silver, salicylic acid, the mercury is not an essential part, but is added to a side chain, so that when the substance is injected into the body, it is easily split off. The dye reaches the diseased cell but the mercury does not. In salvarsan, on the contrary, the arsenic is an essential part of the dye substance and can not be so separated. Consequently it reaches the cell with the dye. Its therapeutic efficiency obviously depends on the ability of its dyestuff guide to penetrate the microorganisms against which the drug is directed. Those which stain most easily are the most susceptible to the destructive action of the arsenic, to wit, the spirochetes of syphilis, anthrax bacilli, the spirilla of recurrent fever, etc. The organisms which resist the stain are uninfluenced by the arsenic; for instance, the waxy envelope about the bodies of the bacilli of tuberculosis is impermeable to the salvarsan dye. It follows that against tubercular disease salvarsan is powerless.

NEW REMEDIES

Salvarsan natrium is a modification of old salvarsan, which is supposed to be superior to neosalvarsan. It is described by Wechselmann[9] as follows: Salvarsan natrium contains 20 per cent. arsenic, the same amount as neosalvarsan. Like the latter, on exposure to the air it changes to a brown color and becomes less soluble and more toxic. It is more soluble than salvarsan and, by so much, easier to use. In eighteen months Wechselmann encountered but four instances of the so-called anaphylactic reaction, all mild. He found the new remedy safe in all stages of syphilis, with doses of 0.3 gm. to 0.45 gm., and suitable for office administration. Two or three injections, one every week, may be given up to a total of forty or fifty. Recurrences were rare. Eruptions, usually resistant to mercury, yielded to persistent salvarsan natrium therapy. In old syphilis the effect on the Wassermann reaction of the blood and of the cerebrospinal fluid varied from prompt to none. For injection Wechselmann prefers 1 per cent. dilutions to the more concentrated.

Dreyfus[2] has used salvarsan natrium with great success in over 450 cases, in from 1 to 1.5 per cent. concentration and in doses rarely exceeding 0.45 gm. Sometimes the drug was used alone, sometimes in

conjunction with mercury. If used alone, it was injected three times a week. If combined with mercury, it was given but twice a week. Over 100 ambulant cases were treated without accident, the patients being required, however, to rest until the morning following the injection. Reactions sometimes occurred, but were never more than slight, transient rises of temperature, diarrhea or attacks of vomiting.

Loeb[16] considers salvarsan natrium as efficient as old salvarsan. His method was to give intravenous injection of salvarsan natrium once a week and intramuscular injections of the mercury salicylate twice a week for a period of four or five weeks.

Pulvis fluens hydrargyri is a mercurial powder proposed by Unna* as a substitute for the less easily prepared and more disagreeable mercurial ointment. It is made by rubbing up metallic mercury with a lycopodium powder, previously soaked in oil of turpentine, in the presence of much air and loosely combined oxygen. The powder which results from the process may be used as such or as an ointment base.

A new method for old remedies was invented by Fischel and Hecht,[17] who obtained intensive mercurial effects by injecting a dose of from 0.015 gm. to 0.04 gm. of mercuric chlorid or of the oxycyanid of mercury (1 to from 200 to 400 c.c. solution) into the cubital vein every three to eight days until eight injections had been given.

SUMMARY OF ARSENOTHERAPY

A few assert that arsenotherapy is efficient without the aid of mercury. This is contradicted by the fact that the search for newer remedies is continued and by the greater prevalence of the combined method. The advocates of arsenotherapy maintain that the method is harmless and is not responsible for the alleged deaths. The opponents answer that, granting the method is falsely accused of death in some cases, the proponents have never produced satisfactory proof of innocence in the remainder; even admitting that the arsenicals merely set a preexisting process in train which causes the death of the patient, the admission of itself proves the method dangerous; and, furthermore, it can not be denied that neurorecurrences have increased with increased arsenotherapy.

Regarding its liability to produce the Herxheimer reaction and the state of anaphylaxis, the debate is about even. Finally, we fail to find in the literature any agreement, even among the advocates of arsenotherapy, as to what constitutes the most efficient dose or concentration. Nicholas and Mutot concluded that while the arsenicals are of unde-

16. Loeb: Deutsch. med. Wchnschr., 1916, lxii, 325.
* Unna: Dermat. Wschnschr., 1915, lx, 337.
17. Fischel and Hecht: Arch. f. Dermat. u. Syph., 1913-1914, cxviii, 813.

niable value they lose in efficiency if not combined with mercury, and that in spite of all dispute, mercury and the iodids still retain their former position and value.

SEROLOGY

Ravaut[18] gives the results of his investigations of the value of the serum test. One result was to convince him that in many quarters too much stress is laid on its evidence. He does not deny any part of its claim to value. He merely deplores the prevailing tendency to regard the test reaction as a mathematical certainty, when the facts justify nothing of the sort. The test, admittedly, possesses many sources of error. Ravaut's experiments bring some into strong prominence. Assuming for the purpose of the argument that the serum test is infallible, Ravaut turned his attention to the personal element in the interpretation, to the influence which personality exerts. Three identical samples were sent to three different serologists and the interpretations of the test reactions compared. He found that 61 per cent. agreed, 36 per cent. varied from positive to doubtful or negative, and 3 per cent. differed absolutely. It was noticeable that the reports conflicted less in tests of avowed syphilitics than of nonsyphilitics.

Ravaut challenges the claim of invariable accuracy for the Wassermann test. He has seen positive reactions persist for years in numbers of instances, despite most vigorous treatment and although no other symptom ever developed. On the other hand, he has seen cases of ocular, cutaneous or visceral disease, unquestionably syphilitic, in which the reaction was invariably negative. Ravaut also claims that there are various conditions which may create a false positive reaction in nonsyphilitic serums, as, for example, injections of autoserum. Of fourteen nonsyphilitics, previously negative, after experimental injections of arsenobenzol 35 per cent. gave positive reactions. Ravaut freely admits that a positive Wassermann test usually means active syphilis and that a negative test does not prove the contrary; but he claims that, while it is desirable to convert a positive reaction into a negative by treatment, it is sometimes impossible. In such cases Ravaut ignores the test and bases his prognosis on other clinical factors. He believes that not even a positive Wassermann reaction can always be accepted if it is not confirmed by other symptoms or evidence.

Keyes[19] insists that the diagnosis of syphilis should not be made on the sole evidence of a Wassermann test. He argues that such methods are illogical. The test is admittedly nonspecific; its results depend too

18. Ravaut: Errors in the Interpretation of the Wassermann Reaction, Ann. de dermat. et de syph., 1914, Series 5, v, 285.

19. Keyes, E. L.: Some Clinical Features of the Wassermann Reaction, Jour. Am. Med. Assn., 1915, lxiv, 804.

much on the technic and too often manifest utterly inexplicable vagaries. Although all agree that a negative test does not disprove the existence of active disease and, much less, that it assures future immunity, a number of alleged cases of reinfection have been reported whose sole foundation was a former negative Wassermann.

Weisenburg[20] says that the Wassermann reaction cannot be made to dominate the diagnosis, even though its great value can be granted without reserve. As a matter of fact, the serum reaction is only a single symptom. Its presence or its absence is a no more indispensable factor in the clinical diagnosis than is any other single symptom. The serum test method has not yet shown why we should discard the ancient dictum that one symptom does not constitute a diagnosis.

Fruhwald[21] has demonstrated by animal experimentation that the blood of syphilitics may contain and may transmit to animals the virus of syphilis, although its serum reaction is consistently negative.

Heimann[22] accepts the evidence of the positive Wassermann test if it can be shown that it has not been influenced by certain nonsyphilitic states which, notoriously, tend to falsify the reaction. On the other hand, the negative test is so regularly in error during certain stages of syphilis and in the presence of many other extraneous factors that it can never be accepted without reserve.

Uhle and Mackenney[23] tested the reliability of the Wassermann reaction from the clinician's standpoint. Seven different serologists, employing different methods, were selected to test the 325 specimens from 292 persons. In every instance identical serums were sent to at least three of the seven operators. The reports were then compared. From 2.5 to 18.1 per cent. of normal and nonsyphilitic persons were reported positive, the percentages varying with the operator. The percentage of positive reports ranged, according to the test method, from 50 to 100 per cent. Five of the seven serologists agreed in 47 per cent. of their total results. It was noteworthy that the serologists who most consistently reported positive tests which clinical expectancy confirmed also most consistently returned doubtful or negative reports when the clinical evidence was doubtful or negative. In 21 per cent. of the total reports there was full agreement; 10 per cent. disagreed completely, and in 61 per cent. of the total reports not more than four conflicted in any one case. The specific antigens gave the smallest number of

20. Weisenburg, T. H.: The Value of the Wassermann Reaction, Jour. Am. Med. Assn., 1915, lxiv, 975.

21. Frühwald: Derm. Wchnschr., 1914, lix, 863.

22. Heimann, W. J.: The Wassermann Reaction as a Clinical Test, with Special Reference to Its Bearing on Matrimony, Jour. Am. Med. Assn., 1915, lxiv, 1463.

23. Uhle, A. A., and Mackinney, W. H.: Comparative Results of the Wassermann Test, Jour. Am. Med. Assn., 1915, lxv, 863.

positive tests, except in two cases. On the other hand, their reactions were most often confirmed by the clinical evidence. It seemed to make no difference in the accuracy of the reaction whether the specimen was collected in sterile or unsterile containers, whether or not the blood was contaminated by virulent strains of the typhoid bacillus, of the *Staphylococcus pyogenes-aureus* or of the streptococcus; whether the specimen was one or several days old; or whether the blood was drawn when the stomach was full or when it was empty. So far as a few cases could show, acidosis did not seem to influence the reaction.

Glomset[24] accepts the unsupported evidence of the serum test without hesitation.

Kolmer and Schamberg[25] conclude that the Wassermann method is not sensitive enough. They often obtained a positive result with cholesterinized serums when, by the Wassermann method, they got a negative. They believe that the sensitized serums furnish reliable proof of the presence of active disease. Nevertheless, they advise that the results should be analyzed in the light of the history and of the clinical signs. Confirming their claim of its greater delicacy, the cholesterin reaction was less easily converted to negative by treatment than the Wassermann.

Hell[7] questions the absolute accuracy of the Wassermann test in its prognosis of congenital syphilis. He found it difficult to change the positive reaction of congenital syphilis to negative even by energetic treatment. He inferred that in congenital cases a positive Wassermann test may not invariably indicate active disease.

CUTANEOUS TESTS AND OTHERS

Noguchi's cutaneous luetin test has been well received in this country, though not abroad. Sherrick[26] reports that both syphilitic and nonsyphilitic cases gave positive cutaneous reactions to luetin inoculation if potassium iodid or any other iodin-containing substance had not been administered just before, at the same time or shortly after the performance of the test.

Klausner[27] includes in his article an interesting review of the general subject of cutaneous tests. Pallidin is a substance obtained by Fischer's method of making extracts from lung tissue.[28] Klausner's

24. Glomset, D. J.: Congenital Syphilis in the Light of the Wassermann Reaction, Jour. Am. Med. Assn., 1915, lxv, 682.

25. Kolmer and Schamberg: Am. Jour. Med. Sc., 1915, cxlix, 365.

26. Sherrick, J. W.: The Effect of Potassium Iodid on the Luetin Reaction, Jour. Am. Med. Assn., 1915, lxv, 404.

27. Klausner: Pallidin Cutaneous Test, Arch. f. Dermat. u. Syph., 1914, cxx, 444.

28. Equal parts of the saline and of tissue, by weight, ground up with glass, centrifugalized, heated to 60 F. for twenty-five minutes, and phenol (carbolic acid) added to make 0.5 per cent.

estimate of its value is as follows: 1. In syphilis, preparations made from tissue rich in spirochetes by a similar technic also give positive cutaneous reactions. 2. A positive reaction is a local, inflammatory infiltration, which reaches its height in thirty-six to forty-eight hours after the inoculation. 3. The pallidin test is specific for syphilis, and especially for the tertiary and late hereditary forms. 4. In precocious, malignant syphilis the reaction is often positive or negative in correspondence to the Wassermann reaction. 5. Visceral gummas are positive to the pallidin test. 6. In cases of parenchymatous keratitis the pallidin test is more often positive than the Wassermann. 7. Gummas of the periosteum and cachexia are often negative to pallidin. 8. Tertiary syphilis and the late, hereditary disease yield a higher percentage of positive reactions to pallidin than to the Wassermann test. Treatment does not greatly influence the pallidin reaction, although if intensive it does sometimes cause it to disappear. Pallidin may excite a positive allergic reaction where previously the serum reaction was negative. The reaction to pallidin is to be interpreted as a phenomenon of anaphylaxis.

Fränkel and Thiele[29] investigated the coagulation test for syphilis, proposed by Hirschfield and Klinger. Nonsyphilitic serum was found to coagulate within fifteen minutes, the time varying with the method employed. Syphilitic serum exhibited a delayed coagulation. The coagulation test, which depends on fixation of the complement, appeared to correspond in most instances to the Wassermann test. Brant[30] drew similar conclusions from his experience with 500 tests. He reports that as a rule the results of the coagulation method and of the Wassermann agreed. When they differed, the history and the clinical signs favored the coagulation test.

Pfeiler and Scheyer[31] recomended the employment of hemolysin and hemagglutinin as indicators of complement fixation in syphilis and as a parallel method to the Wassermann. They reported several cases of suspected syphilis in which these methods were positive when the Wassermann was negative.

CILIA A DISTINGUISHING MARK OF TREPONEMA

Fontana[32] reports a new method of staining by means of which he succeeded in demonstrating that the treponema possess cilia. He estimates that the length varies from one to seven times that of the windings of the organism; that the cilia occur in both straight and spiral forms; that they may be at one or at both ends of the organism;

29. Fränkel and Thiele: München. med. Wchnschr., 1914, lxi, 2095.
30. Brant: Deutsch. med. Wchnschr., 1915, xli, 915.
31. Pfeiler and Scheyer: München. med. Wchnschr., 1915, lxii, 393.
32. Fontana: Derm. Wchnschr., 1914, lix, 1367.

that they are exceedingly thin; and that, though they stain weakly, they nevertheless stain sufficiently to be photographed. Most specimens of cilia do not end in a point but in a more or less well-developed, club-shaped swelling, three or four times as thick as the cilia itself, which stained moderately well. This last observation Fontana considers unique.

MANIFESTATIONS OF CONGENITAL SYPHILIS

De Aja[33] believes that congenital syphilis is in reality extraordinarily frequent. His cases varied in age from 8 to 53. Examples of the so-called late or adult syphilis were not rare. Usually the history in such cases revealed the existence of syphilis in the parents. Their own most frequent symptom of the inherited infection was disease of the long bones. De Aja believes that these cases of late manifestations of inherited syphilis are frequently unrecognized, because the observer fails to take into account every factor connected with the lesions, the symptoms and the history and because he does not comprehend how frequent inherited syphilis really is or how it may make itself manifest.

In their discussion of the manifestations and the diagnosis of congenital syphilis Soldin and Lesser[34] manifest that comfortable reliance on the unvarying truth of the Wassermann reaction which Ravaut so deplored. The writers examined a large number of infants and children who were admitted to the hospital for nonsyphilitic diseases and who, therefore, showed none of the ordinary signs of syphilitic inheritance. In such cases snuffles were never pronounced, skin rashes were few, and epitrochlear glands were barely palpable. Enlargements of the spleen or liver were the most important symptoms of their syphilitic inheritance. Many children showed not the slightest sign of syphilis, not even a positive serum reaction. Nevertheless, Soldin and Lesser unhesitatingly proclaimed them syphilitic because their mothers invariably yielded positive tests. They concluded that in children, even when corroborative evidence fails, bare suspicion is sufficient reason for testing the mother's blood. If the result is positive, the child must be regarded as a victim of inherited syphilis.

Haberman[35] calls attention to the fact that although syphilis may be one of the great inherited causes of degeneracy, it is not the sole cause. Therefore, to avoid harmful error, the possibility of a nonsyphilitic origin can never be ignored.

Vignoli-Lutati[36] maintains that many cases in which the enlarged cervical glands break down and produce scars are wrongly attributed

33. De Aja: Actas Dermo-Sif., 1914, vi, 193.
34. Soldin and Lesser: Deutsch. med. Wchnschr., 1915, xli, 429.
35. Haberman, J. V.: Hereditary Syphilis, Jour. Am. Med. Assn., 1915, lxiv, 1141.
36. Vignoli-Lutati: Arch. f. Dermat. u. Syph., 1914, cxx, 376.

to tuberculosis. Yet no proof of tuberculosis has ever been demonstrated. Because of their occurrence in association with congenital syphilis, because tuberculosis has not been proved and because the symptoms respond promptly to antisyphilitic treatment, Vignoli-Lutai is convinced that the true cause is not tuberculosis but inherited syphilis.

TRANSMISSION OF SYPHILIS

Glomset[24] is of the opinion that the syphilitic virus may be transmitted to the fetus by way of the placenta and that the infection usually occurs late in gestation.

Fordyce[14] states that the manner of fetal infection is indirecet, that is, through the mother; that the later the stage of the disease in the mother, the greater chance that the fetus will escape; and that he believes that the spirochetes pass from the mother through the placenta to the blood of the child.

As has just been noted, Soldin and Lesser maintain that even though the offspring show no visible signs and even though they manifest negative Wassermann reactions, the positive serum tests of their mothers is sufficient to prove that the children are syphilitic. The lack of evidence in the children, they say, is due to immunization during intrauterine life, with a consequent prevention or hindrance to the further development of spirochetas in the offspring.

Trinchese[37] has collected data concerning congenital syphilis from various sources, which he interprets as follows:

1. It is impossible for the fetus to immunize the mother (Colles' law). Paternal infection of the fetus, alone, does not exist. Moreover the fetus has never been shown to possess immunizing substances. 2. The immunization of the fetus by the mother (Profeta's law) is not an infallible occurrence. 3. The earlier the infection of the fetus, the more rapid the development of a septic syphilitic process which is fatal within six months. 4. The mother may have a positive Wassermann and the fetal tissues may abound in spirochetes, and yet the fetal reaction will be negative, because the fetus builds no reaction substance until about its eighth month. After the eighth month the fetal blood for the first time begins to respond positively. 5. If infection occurs in the last weeks of gestation, the infant may possess neither clinical symptoms nor a positive serum reaction, because the time permitted the spirochetes for incubation has been too short. Such cases were once considered immune. In fact they are the cases in which the late manifestations of inherited disease develop. 6. If the mother is syphilitic, neither the absence of clinical signs nor of a positive serum reaction is

37. Trinchese: Deutsch. med. Wchnschr., 1915, xli, 555.

positive proof of health. 7. Four possible eventualities confront the offspring of syphilitic mothers, which in the order of their gravity are clinical freedom and a negative test; clinical freedom and a positive test; clinical signs and a negative test; clinical signs and a positive test. The last is inevitably fatal.

We have considered above the possibility of transmission only by the mother with a positive Wassermann reaction. Frühwald's[38] experimental inoculation of a syphilitic rabbit's testicle indicates that the blood of a syphilitic mother, without either visible signs or a positive Wassermann reaction, may, nevertheless, be infectious.

The advent of the Wassermann test has not caused Keyes[19] to alter his views concerning the marriage of syphilitics. He can see no reason for changing the old rules.

Heimann[22] will not consent to the marriage of syphilitics so long as the serum reacts positively; so long as a sufficient period has not elapsed, without symptoms, after disappearance of the positive reaction under adequate treatment; or so long as the serum gives a positive response to provocative injections of salvarsan.

Nicholas and Mutot[4] recommend the retention of the old rules concerning syphilitic marriages.

SUMMARY

Three broad conclusions may be drawn from this exposition of the literature on the subject of syphilis:

1. Today all parties concede the right of the arsenicals to a place in the sun of syphilitic therapeusis. Nor does the concession invalidate the claim that mercury and the iodids have lost nothing of their original worth (Nicholas and Mutot).

2. The Wassermann and the other serum tests are seated more firmly in their original position as efficient aids to diagnosis, but have failed signally to deprive clinical methods of their old importance.

3. In short, the newer methods of diagnosis and of treatment have strengthened our hands immeasurably. The older methods have held their own. Combined, they mark a noteworthy advance in the subject of syphilis which neither could accomplish alone.

38. Frühwald: Dermat. Wchnschr., 1915, lx, 513.

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